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STREPTOCOCCIC AND PNEUMOCOCCIC INFECTIONS OF THE NOSE AND THROAT IN YOUNG ADULTS

INCIDENCE, EPIDEMIOLOGY AND CLINICAL FEATURES

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We have been impressed by the lack of detailed and accurate information in medical textbooks about the most common diseases which the average American physician is called on to treat. For this reason, an attempt has been made to gather together some of the observations made in our own work on tonsillitis, pharyngitis, laryngitis and paranasal sinusitis.

It is appreciated that the clinical conditions mentioned here seldom occur alone. They are most often a part of a diffuse involvement of the upper respiratory passages. Often they are complications of other diseases. An attempt has been made, however, to separate them from ordinary uncomplicated colds, influenza, bronchitis and pneumonia. Scarlet fever enters into the discussion as a part of the hemolytic streptococcus infections of the nose and throat. Diphtheria, Vincent's angina and syphilitic infections are not considered here.

INCIDENCE

In a nursing population averaging 1,034, over a five year period, the average monthly number requiring rest in bed because of these diseases was 27.21—approximately 2.6 per cent of the entire group. The peak was in January, February, March and April—averaging 4 to 5 per cent—with a moderate drop in May and a sharp drop in June, July and August to about 1 per cent (chart 1). In the fall months the number gradually rose, but not to the level of January and the early spring months. It is interesting to note how closely this curve parallels that of the finding of hemolytic streptococci in 1,115 cultures of material taken at all seasons of the year from the throats of our own patients who presented all types of respiratory infections (chart 2).

Also of interest is the fact that simple rhinitis and acute diffuse respiratory infections, such as influenza and grip, rose sharply during the fall months and outstripped sore throat and sinusitis in December, then fell below these during the remainder of the year. The total monthly incidence of *incapacitating* infections of the upper respiratory passages exclusive of pneumonia averaged 4 per cent for the year. While this figure may be unusually high because of the frequent exposures of this particular group of young adults, it indicates the enormous number of respiratory infections in this country. In children the incidence is probably even higher.

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DISABILITY CAUSED BY THE AVERAGE ATTACK OF SORE THROAT OR SINUSITIS

In a previous report[1] we showed that the average total time lost by a Cook County Hospital nurse is 75.7 days in a three year period of training—approximately 7 per cent of her total time—20.46 days of which (27 per cent) is from the afore-

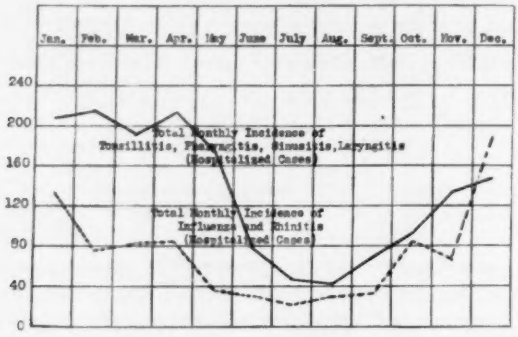

Chart 1.—Incidence of respiratory infections in a nursing group averaging 1,034 members over a five year period. The number off duty with tonsillitis, pharyngitis, laryngitis and sinusitis averaged 27.21 per month—2.6 per cent of the nursing population. The number off duty with influenza, grip and simple rhinitis averaged 14.53 per month—1.4 per cent of the nursing population.

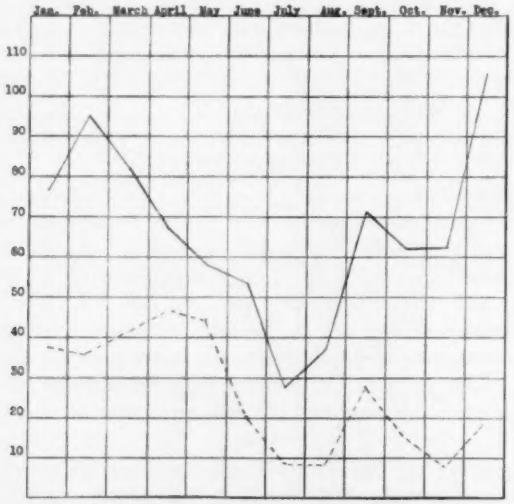

Chart 2.—Monthly distribution of 1,115 cultures of material taken from the throats of persons with infections of the upper respiratory tract or exposed to such infections between Jan. 1, 1937 and Jan. 1, 1940. The number of cultures negative for hemolytic streptococci (———) was 800; the number positive for these organisms (.....) was 315.

mentioned diseases. The average time lost per attack of sore throat and sinusitis caused by hemolytic streptococci was 16.85 days, and the time lost because of such

1. Rhoads, P. S., and Afremow, M. L.: Clinical and Statistical Study of Sore Throat in Young Adults, Arch. Path. **26**:403 (July) 1938.

conditions not associated with hemolytic streptococci was 14 days. Hemolytic streptococci were responsible for about two thirds of the cases of sore throat and sinusitis.

In comparing the sore throat groups with a series of patients with scarlet fever who were of the same age and studied at the same time as those with sore throat (table 1) it was seen that cases of sore throat caused by hemolytic streptococci were complicated more than twice as frequently as cases of sore throat not caused by hemolytic streptococci, and almost exactly as frequently as the cases of scarlet fever. Numerically, the complications were quite similar, but the complications of the cases of scarlet fever were more severe, including two deaths, and renal involvement appeared more frequently.

Though full cognizance is taken of the fact that scarlet fever is a more serious disease than hemolytic streptococcus sore throat without a rash, insistence on strict quarantining of patients with scarlet fever for twenty-eight days and disregard

TABLE 1.—*Comparison of Complications in Three Groups of Nurses with Sore Throat*

Sore Throat Caused by Hemolytic Streptococci (159 in Group)	Cases	Percentage	Sore Throat Not Associated with Hemolytic Streptococci (81 in Group)	Cases	Percentage	Scarlet Fever (60 in Group)	Cases	Percentage
Sinusitis	43	27.0	Sinusitis	5	6.2	Sinusitis	6	10.0
Cervical adenitis	13	8.2	Cervical adenitis	2		Cervical adenitis (1 deep cervical abscess)	5	8.3
Otitis media	6	3.8	Otitis media	1		Otitis media	4	6.7
Rheumatic fever	5	5.7	Rheumatic fever	1		Rheumatic fever	1	6.7
Persistent tachycardia	2		Persistent tachycardia	1		Acute polyarthritis	2	
Reactivation of rheumatic fever	1		Persistent pharyngitis and tonsillitis	2		Persistent tachycardia	1	
Rheumatoid arthritis	1		Persistent asthenia	1		Acute nephritis (1 death)	3	5.0
Persistent tonsillitis and pharyngitis	4	2.5	Bronchitis	2		Transient albuminuria	6	10.0
Acute nephritis	1		Peritonsillar abscess	1		Hemolytic streptococcus septicemia (death)	1	
Persistent asthenia	2		Lumbar myositis	1		Pyelitis	1	
Peritonsillar abscess	1		Total	17	21.0	Acute enteritis	1	
Erysipelas	1					Acute appendicitis	1	
Pleuritis	1					Bronchitis	1	
Lacrimal abscess	1					Total	33	55.0
Appendicitis or mesenteric lymphadenitis	1							
Hemolytic streptococcus carrier	1							
Total	84	52.8						

of quarantine for patients with sore throat without a rash still seem somewhat inconsistent.

NORMAL BACTERIAL FLORA OF THE THROAT AND NOSE

The extremely difficult problem of establishing what bacteria are found in the throat and nose under normal conditions must be solved before one can impute pathologic significance to certain organisms in a culture containing a number of varieties. No claim to completeness is made for our studies. Young adults who were on duty and supposedly not ill were chosen as subjects. It was often found that some of them had slight fever and slight leukocytosis. Examinations of the noses and throats of these often revealed considerable inflammation. The examinations of the total group were scattered through the months of November, January, February, March, April, May and June. For that reason the incidence of hemolytic streptococci may be a little higher than average. A typical cross section of the entire population would require a much larger series.

The smears of material from the throats (table 2) were stained with dilute gentian violet, so that Vincent's organisms could be more easily distinguished. Thus the bacteria are divided only according to their morphologic character, not according to their staining properties. The well known fact that spirilli and fusi-

form bacilli appear in a high percentage of throats and that a diagnosis of Vincent's angina can be supported only by the finding of large numbers of these organisms is again demonstrated.

The cultures of material from the throats (table 3) were made by rubbing a cotton swab over the pharynx and tonsils, or tonsillar fossae, then transferring the inoculum to a blood agar plate (p_H 7.4), where it was spread over the surface by a wire spreader or bent glass rod. They were read at twenty-four hours. It is seen that cocci causing greening on blood agar were found in every culture. These were known to be Streptococcus viridans and pneumococci, but no differentiation was attempted in this series. They are mentioned because it seems still not to

TABLE 2.—*Analysis of Findings in Smears of Material Taken from Throats of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)* *

Organisms Noted in 78 Smears Made †	Times Found	Percentage
Cocci (no differentiation attempted)	77	99
Bacilli not with the morphologic character of fusiform bacilli (no further differentiation)	61	78
Fusiform bacilli	22	28
Spirilli	10	13
Mycelia	5	6

* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

† None of the patients had Vincent's angina. No connection was found between the presence of spirilli and fusiform bacilli and hemolytic streptococci in cultures of the same material.

TABLE 3.—*Analysis of Findings in Cultures Made from Material Taken from Throats of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)* *

Organisms Noted in 85 Cultures Made on Blood Agar	Times Found	Percentage
Cocci causing greening on blood agar (no further differentiation)	85	100
Staphylococci	59	70
Albus — 40 times		
Albus haemolyticus — 8 times		
Aureus — 6 times		
Aureus haemolyticus — 5 times		
Gram-negative micrococci chiefly Micrococcus catarrhalis and Micrococcus pharyngis siccus	54	64
Hemolytic streptococci	17	20
Sarcinae	22	26
Anhemolytic streptococci	9	11
Diphtheroids	6	7
Large gram-positive bacilli	6	7

* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

be appreciated by all physicians that colonies of Str. viridans are almost invariably present in material properly taken from throats in this geographic area.

Staphylococci and gram-negative micrococci were found in the majority of cultures. Anhemolytic streptococci, while found infrequently, were thought to have no special pathologic significance. Since our chief interest in this study was in hemolytic streptococci, the significant associated clinical findings in those persons found to be harboring them are summarized in (table 4). Of 4 persons having large numbers of hemolytic streptococci—as indicated by a 3 plus or a 4 plus notation—3 had been quite recently exposed to scarlet fever. Two of these had definitely inflamed throats. The fourth was convalescent from scarlet fever. The majority of the hemolytic streptococcus carriers with less strongly positive cultures had inflamed throats and slightly elevated leukocyte counts and some had slight fever. The impression gained here that hemolytic streptococci rarely occur in large numbers in perfectly normal persons had support in studies to be shown later.

Cultures of material from the noses (table 5) were made in exactly the same way, the swab being introduced at least 1 inch (2.5 cm.) into each nostril. Staphylococci were found in every culture. No special pathologic significance of the hemolytic forms appeared in this series, although it is our belief that the hemolytic Staphylococcus aureus in rare instances causes sinus infections and sore throat. No influenza bacilli were encountered, although they were occasionally present in cultures from persons with "diffuse upper respiratory infection."

TABLE 4.—*Clinical Data on Carriers of Hemolytic Streptococci Among Eighty-Five Supposedly Normal Young Adults*

Kind of Growth	Temperature, F.	White Blood Cell Count	Clinical Findings
3+	98.6	8,600	Exposed to scarlet fever two days previously; sore throat for two days
3+	98.6	8,200	Exposed to scarlet fever two days previously; throat acutely inflamed; chronic sinusitis
4+	98.6	No count	Exposed to scarlet fever two days previously; no pathologic condition found
4+	99.4	6,900	Had scarlet fever one month ago; throat still inflamed
2+	98.2	10,650	Inflamed tonsil; pains in joints
2+	99.8	13,200	Throat and nose inflamed
2+	98.6	9,000	Acute sore throat six weeks ago; pharynx still inflamed; chronic sinusitis
2+	99.2	10,800	Chronic sinusitis; continued pains in joints; throat inflamed
1+	98.0	5,100	Tonsillectomy because of arthritis three months ago; none at present
1+	98.6	10,300	Cold three weeks ago; throat still slightly inflamed; albuminuria
1+	99.4	No count	Chronic sinusitis; throat and nose inflamed
1 Col.	97.6	7,800	No pathologic condition
1 Col.	98.0	11,100	No pathologic condition
3 Col.	98.0	10,000	Severe sore throat three months previously; throat still slightly inflamed
5 Col.	99.2	10,550	Throat slightly inflamed; has a cold
2 Col.	98.4	6,200	No pathologic condition
7 Col.	98.6	6,300	No pathologic condition; recent exposure to scarlet fever

TABLE 5.—*Analysis of Findings in Cultures of Material Taken from Noses of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)* *

Organisms Noted in Cultures on Blood Agar (75 Had a Growth)	Times Found	Percentage
Staphylococci	75	100
Albus 58 times		
Albus haemolyticus 19 times		
Aureus 10 times		
Aureus haemolyticus 5 times		
Citreus 1 time		
Diphtheroids	10	13
Hemolytic streptococci	4	5
Anhemolytic streptococci	4	5
Green-forming cocci	5	7
Gram-positive bacilli (not further differentiated)	2	3
Gram-negative diplococci (not further differentiated)	2	3

* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

The clinical findings in those members of the series harboring hemolytic streptococci, anhemolytic streptococci and green-forming cocci in their noses are given in table 6. No *heavy* growth of hemolytic streptococci was found. Of the 4 persons in whose cultures they were present, 2 appeared to have normal mucous membranes. One of these, however, had been exposed to scarlet fever two days previously. The other 2 had inflammation of the nose or pharynx. Anhemolytic streptococci and green-forming cocci appeared to be unassociated with pathologic conditions in only 3 of 9 cultures. It is our belief that the organisms of the groups just mentioned rarely occur in the noses of normal persons.

CARRIERS OF HEMOLYTIC STREPTOCOCCI

That hemolytic streptococci are readily spread from one person to another is shown by the fact that 20 per cent of a group of normal young adults harbored hemolytic streptococci in their throats, while 41 (53.4 per cent) of a group of 77 persons in our own practice who were directly exposed to scarlet fever were found to have these organisms in their throats. In this same connection a study of

TABLE 6.—*Clinical Data on Supposedly Normal Young Adults Who Were Found to Harbor Streptococci in Their Noses*

Kind of Growth	Temperature, F.	White Blood Cell Count	Clinical Findings
			Carriers of Hemolytic Streptococci
1+	98.4	9,550	Acute pharyngitis 2 days after culture was taken
1+	98.6	7,650	No pathologic condition
2+	99.4	6,000	Scarlet fever 1 month previous; nasal mucosa still inflamed
1 Col.	98.2	6,300	Exposed to scarlet fever 2 days before; no pathologic condition
			Carriers of Anhemolytic Streptococci
3+	98.6	7,800	No pathologic condition
2+	98.4	7,250	Just over a cold; mucous membranes red
4+	98.6	8,600	Chronic paranasal sinusitis
1+	99.2	No count	No pathologic condition
			Carriers of Green-Forming Cocci
1+	98.4	8,200	No pathologic condition
3+	99.4	10,800	Chronic sinusitis
4+	98.9	10,000	Chronic sinusitis
1+	99	8,900	Chronic sinusitis; acute cold 1 week ago
1+	98.6	9,000	Chronic sinusitis; last acute flareup 6 weeks ago

TABLE 7.—*Study of Two Hundred Nurses at Cook County Children's Hospital Who Had Cultures Made of Material from Nose and Throat When They Began Duty and at Weekly Intervals Thereafter*

	Number	Percentage
Total number of cultures	1,600	
Cultures positive for hemolytic streptococci	855	53.4
Cultures negative for hemolytic streptococci	745	46.6
Cultures 3+ or 4+ for hemolytic streptococci	82	5.1
Cultures 2+ for hemolytic streptococci	220	13.7
Cultures 1+ for hemolytic streptococci	553	34.6
Total number of nurses for whom cultures were made	200	
Nurses whose initial culture showed hemolytic streptococci	94	47
Nurses whose initial culture showed no hemolytic streptococci	106	53

Of the 106 nurses who entered with a negative culture, 77 (72.6 per cent) had hemolytic streptococci in their throats or noses before they left the Children's Hospital. (An average of eight cultures were taken per nurse.) Twenty-nine continued to have negative cultures throughout their stay.

200 nurses chosen alphabetically from the Cook County Children's Hospital is of interest (table 7).

In a previous study [1] we had found that sore throat due to hemolytic streptococci occurred more frequently in nurses on duty in the Children's Hospital than in any other division of Cook County Hospital save the Contagious Hospital. Dr. M. L. Blatt and his associates there wished to learn whether nurses were spreading hemolytic streptococci among the patients. As a part of this study, all nurses had cultures made of material from the nose and throat, on blood agar, when they began service and at weekly intervals thereafter. An average of eight cultures were made per nurse on the group selected for study, making 1,600 cultures

in all. Forty-seven per cent of the nurses assigned to the Children's Hospital had cultures showing this type of streptococci when they arrived, indicating the high rate of exposure throughout the entire hospital. Of those who entered free of these organisms, 72.6 per cent had acquired them, as revealed by cultures, at some time before they finished their service. However, only 5.1 per cent of the total number of cultures were strongly positive for hemolytic streptococci, as indicated by a 3 or 4 plus recording; of the remaining ones, 13.7 per cent were 2 plus and 34.6 per cent 1 plus.

A study of the physical condition of the nurses who harbored hemolytic streptococci (table 8) revealed that 47 of the group of 200 nurses had at some time one or more 3 plus or 4 plus cultures. Thirty of this 47—almost two thirds—had an active infection of the nose or the throat at the time the culture was taken or had been off duty with acute sore throat or sinusitis within six weeks of that time, and 20 of them were sick enough that they had to go off duty.

Sixty more nurses of the group of 200 had one or more 2 plus cultures but never any with heavier growths. Only three of them were found to have frankly

TABLE 8.—*Study of Physical Condition of Nurses Whose Cultures Were Positive for Hemolytic Streptococci*

	Number	Percentage
Total number of nurses studied	200	
Nurses having at some time 3+ or 4+ cultures	47	23.5
Nurses having 3+ or 4+ cultures who had pathologic findings in nose and throat	30	
All of these had an active infection at the time material was taken for culture or had been off duty within six weeks of that time with acute sore throat or sinusitis		
Nurses having 3+ or 4+ cultures who had to go off duty during their service at the Children's Hospital because of sore throat or sinusitis	20	
These twenty nurses lost 132 days off duty, an average of 6.6 days per nurse		
Nurses having 2+ but not 3+ or 4+ cultures	60	30% of plus culture
Nurses with 2+ cultures who had pathologic findings in nose and throat	3	
The time lost because of sore throat and sinusitis in this group was 16 days		

pathologic changes in the throat or the nose, and only these nurses were required to go off duty because of infection in these regions. The physical status of those with 1 plus cultures only was not determined, because they were not required to report for examination. Our records do not show that any were forced to go off duty because of infection of the upper respiratory passages. Thus it appears that the majority of those persons who have large numbers of hemolytic streptococci in the throat or the nose have active infection in these areas or are convalescent from such infection.

How much of a menace those persons constitute toward the persons with whom they are in contact cannot be determined from this study. However, if an analogy may be drawn with another disease characterized by sore throat due to hemolytic streptococci, scarlet fever, it will be seen that the rate of spread to direct contacts is alarmingly high. At the Cook County Contagious Hospital 21 per cent of the patients with scarlet fever studied over a thirteen month period had another member of the immediate household in the hospital with scarlet fever during their period of hospitalization or within a few days of the time they returned home.[2]

2. Rhoads, P. S.; Tucker, W. H., and Rappaport, B.: Management of Scarlet Fever Contacts, J. A. M. A. **117**:1063 (Sept. 27) 1942.

It is seen in table 9 that often secondary cases occur after a patient has been discharged from the Contagious Hospital and returns home, at the end of twenty-eight days, as a so-called healthy carrier. How long such persons may remain carriers has not been determined in our studies, but we found by examining the records of the past five years at the Evanston Hospital that 63 per cent of the patients with scarlet fever had positive cultures at the end of their twenty-eight day quarantine. One of our private patients had strongly positive cultures for four months.

While the great practical difficulty of quarantining all persons who harbor large numbers of hemolytic streptococci in the nose and throat is thoroughly appreciated by those who have tried to quarantine even an occasional one, the necessity of dealing more adequately with the carrier problem is easily apparent. In cooperation with Dr. John Coulter, Dr. Alfred Lewy, of the staff of the Cook County Nurses' Infirmary, tried treating the nasopharynx and pharynx daily with ultraviolet rays, without ridding the throats of hemolytic streptococci. Giving sulfanilamide over as long periods as the nurses would take the drug was equally unsuccessful.

TABLE 9.—*Typical Sequence of Cases of Scarlet Fever in Two Families of the Cook County Hospital Series (From Rhoads, P. S.; Tucker, W. H., and Rappaport, Benjamin: Management of Scarlet Fever Contacts, J. A. M. A.* **117**:*1063-1065 [Sept. 27] 1941)*

Name	Age	Onset	Admission	Discharge
First family:				
Frank	6	9/14/39	9/18/39	10/13/39
George	10	10/17/39	10/19/39	11/14/39
Geraldine	8	10/18/39	10/19/39	11/18/39
Lee	4	11/ 1/39	11/ 2/39	11/29/39
Paul	8 mo.	11/ 9/39	Cared for at home	
Second family:				
Lillian	9	12/ 9/39	12/11/39	1/ 6/40
Clifton	10	1/ 9/40	1/13/40	2/ 6/40
Mildred	13	1/14/40	1/15/40	2/11/40

In 1941 Schoenbach, Enders and Mueller[3] reported that tyrothricin (an extract from Bacillis brevis of Dubos) in a dilution of 1 : 100 in physiologic solution of sodium chloride with 2.5 per cent glycerin, when sprayed onto the rhinopharynx, was effective in terminating the carrier state in 5 persons convalescent from scarlet fever. This method was tried by us in the treatment of 2 nurses, but cultures of material from their throats showed no change in the numbers of hemolytic streptococci.

Placing carriers of hemolytic streptococci in environments in which they do not encounter more streptococci is an important part of the regimen to rid them of the carrier state.

Daily spraying of the throat and the nose with a 2.5 per cent solution of sodium sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or of sodium sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) has appeared to terminate the carrier state in 9 persons.[4] In others a combination of spraying of the nose and throat with a solution of a sulfonamide compound and administering of sulfadiazine by mouth has appeared to help. But none of these methods is uniformly effective.

3. Schoenbach, E. B.; Enders, J. F., and Mueller, J. H.: The Apparent Effect of Tyrothrycin on Streptococcus Hemolyticus in the Rhinopharynx of Carriers, Science **94**:217 (Aug. 29) 1941.

4. This statement is based on work to be reported in another article.

INCIDENCE AND CLINICAL SIGNIFICANCE OF STREPTOCOCCUS VIRIDANS AND PNEUMOCOCCI IN CULTURES OF MATERIAL FROM THE NOSE

In a series of 591 cultures (table 10) of material taken from the noses of persons suffering from infections of the upper respiratory tract at all seasons of the year, only 73 (12.3 per cent) were found to contain green-forming cocci. An estimation

TABLE 10.—*Analysis of Data on Nasal Cultures in Which Green-Forming Cocci Were Found*

	Number	Percentage
Total number of cultures	591	
Number in which green-forming cocci were found	73	12.3
Green colonies unidentified further — 18 times		
Streptococcus viridans — 37 times		
Pneumococcus — 21 times		
Type III — 6 times		
Undetermined — 5 times		
Type XXIII — 3 times		
Type XXII — 2 times		
Type VI — 1 time		
Type XXV — 1 time		
Type XIX — 1 time		
Type XI — 1 time		
Type VII — 1 time		
Number of cultures containing green-forming cocci associated with clinical findings that indicated active disease	72	98.6
Number of cultures containing green-forming cocci from frankly allergic persons with exacerbation of chronic rhinitis or sinusitis	46	63
Number of cultures from children 12 years or under	115	
Number of cultures positive for green-forming cocci	21	18.3
Number of cultures from adults	476	
Number positive for green-forming cocci	52	10.9

TABLE 11.—*Portion of Summarized Clinical Findings in Persons with Streptococcus Viridans or Pneumococci in Nasal Cultures*

Date	Initials	Age	Green Colonies Unidentified	Str. Viridans	Pneumococcus	Clinical Findings	Temperature, F.
3/20/39	M. A.	8	.....	++++	.....	Acute pharyngitis and rhinitis in allergic child; white blood cell count 15,650	102
4/11/39	J. B.	A	.....	+	.....	Acute sinusitis (chronic allergic rhinitis)	98.6
4/10/39	M. A.	A	++	.....	.....	Acute flareup of chronic allergic sinusitis	99.2
4/29/39	F. T.	11	.....	.....	Type 19 +++	Acute exacerbation of chronic rhinitis; albuminuria	99.4
5/ 4/39	M. N.	A	.....	++	.....	Acute rhinitis with prostration	99.2
5/15/39	M. S.	A	++	.....	.....	Chronic allergic rhinitis and iritis	99.0
5/19/39	B. C.	4	+++	.....	.....	Acute rhinitis and tonsillitis	102.4
5/25/39	M. S.	A	++++	.....	.....	Acute flareup of chronic allergic rhinitis; no fever	.....
6/29/39	J. W.	8	+	.....	.....	Acute flareup of chronic allergic rhinitis	101.2
10/ 8/39	K. W.	A	.....	.....	Type 3 +++	Acute sinusitis	101.0
10/14/39	M. L.	A	.....	.....	Type 3 +++	Chronic allergic state with acute sinusitis and asthma	.....
11/20/39	A. V.	6	.....	.....	Type 11 ++	Acute pharyngitis and rhinitis	103.0

of the clinical significance of these organisms in this series was attempted. From 58 of the 73 cultures in which the green-forming cocci were found, four to six colonies were transferred to tubes of broth in which pneumococci were proved to grow well and the cultures were examined microscopically and for solubility in bile. In this way 21 (36.2 per cent) of the 58 cultures were identified as pneumococci and the remainder as Str. viridans. The two organisms were seldom found together in the nose.

Type III was the most frequent type of Pneumococcus found—the rest of the 21 cultures being widely scattered among the other types. None of the patients had pneumonia at the time the cultures were taken—which probably accounts for the fact that types I and II were not encountered.

The striking facts brought out by the clinical findings in these persons (table 11) are that nearly all persons harboring green-forming cocci in the nose are ill or recovering from acute infectious of the nose and the throat and that a high percentage are frankly allergic. Whether the infection with these organisms is the result of the allergic state or the cause of it was not determined in our studies. Another interesting finding was the much greater frequency of green-forming cocci in children's noses than in those of adults. We had the impression that this was true but had no confirmation of the fact until this study was made. A possible explanation may lie in the shorter distance in children from the nasopharynx to the nares. Possibly the swab more often reaches the natural habitat of these organisms in young persons. Our results are in agreement with those of Jacobson and Dick,[5] who found that green-forming cocci were rarely present in nasal cultures in the absence of acute rhinitis and/or paranasal sinusitis. They also noted that children harbored these organisms in the nose more frequently than adults.

SUMMARY

In a nursing group averaging 1,034, over a five year period the average number off duty at all times because of infection of the upper respiratory tract was 4 per cent of the entire number. Of the ones so disabled, 65 per cent were thought to have bacterial infections, including acute tonsillitis, pharyngitis, laryngitis, purulent rhinitis and paranasal sinusitis. The other 35 per cent had simple rhinitis, influenza or grip—all thought to be virus infections. The peak of the bacterial infections of the nose and throat was in January, February, March and April, while the peak of the virus infections was in December—at which time the incidence always rose sharply.

Among a group of nursing students studied through their three years of training, the average time lost because of bacterial infections of the nose and throat was 20.46 days—27 per cent of the total time lost by them because of illnesses of various types.

Sixty-six per cent of these infections appeared to be caused by hemolytic streptococci. The average time off duty caused by each attack of sore throat or sinusitis due to hemolytic streptococci was 16.85 days.

The complications resulting from these infections caused by hemolytic streptococci were almost as numerous as those in a series of patients with scarlet fever of the same age, studied over the same period, though not as serious.

Among normal young adults (chiefly medical students) 20 per cent were found to harbor hemolytic streptococci. Those whose cultures contained large numbers of hemolytic streptococci were found often to have inflammation of the throat or the nose, slight fever and leukocytosis. Others were convalescent from recent infections. In no instances were normal-appearing mucous membranes found to contain hemolytic streptococci in large numbers.

Green-forming cocci (Str. viridans and/or pneumococci) were found in every culture made of material swabbed from the throat. They were therefore regarded as normal inhabitants of the pharynx.

5. Jacobson, L. O., and Dick, G. F.: Normal and Abnormal Bacterial Flora of the Nose. J. A. M. A. **117**:2222 (Dec. 27) 1941.

However, green-forming cocci, as well as hemolytic streptococci, when found in cultures of material from the nose were nearly always associated with frank infection of the nasal mucosa, the sinuses or the nasopharynx.

Among persons directly exposed to hemolytic streptococcus infections (such as those coming in contact with patients suffering from scarlet fever or nurses on duty in children's hospitals) the incidence of hemolytic streptococci in cultures of material from the throat and the nose was more than 50 per cent, while in an average group of young adults it was 20 per cent.

There is abundant evidence that so-called healthy carriers spread scarlet fever. The assumption is reasonable that carriers of nonspecific hemolytic streptococci also spread infection to those with whom they come in contact.

No uniformly successful method of ridding carriers of hemolytic streptococci has been found by us.

While green-forming cocci are regarded as normal inhabitants of the throat, they were rarely found in the nose except in association with definite infection of the nasal mucosa or sinuses. They were found more frequently in children's colds than in those of adults.

CONCLUSIONS

Hemolytic streptococci are responsible for about two thirds of the attacks of tonsillitis, pharyngitis, laryngitis and sinusitis in young adults. These diseases are probably more frequent and cause more disability than any other diseases affecting this age group.

Persons who harbor large numbers of hemolytic streptococci in their throats and those who harbor these organisms or green-forming cocci in their noses usually have an active infection or are convalescent from an active infection.

The serious results of allowing carriers of hemolytic streptococci to circulate in groups of young adults, such as soldiers in barracks, is apparent.

Cultures of material from the throat and the nose on blood agar are inexpensive and easy to make, and not difficult to interpret. They should be made in all instances of infection of the throat or the nose.

Serious consideration should be given to quarantining of persons harboring hemolytic streptococci in the throat or the nose or green-forming cocci in the nose. More effective methods of ridding carriers of these organisms urgently need to be devised.

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A RENAL CONCENTRATION TEST USING SOLUTION OF POSTERIOR PITUITARY

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The ability of the renal tubules to concentrate urine is the basis of several clinical tests of renal function in use today. Fishberg [1] expressed the belief that the specific gravity tests are the most useful tests of renal function available for the general practitioner and general hospital use. Sodeman and Engelhardt [2] recently advocated use of solution of posterior pituitary for a renal function test. This test utilizes the antidiuretic principle of the posterior lobe of the pituitary gland and enables one to perform a renal concentration test without prolonged restriction of the intake of fluids. It has the further advantage of giving reliable results in the presence of ascites or cardiac edema, where other concentration tests cannot be used because of the impossibility of depriving the kidneys of the excess fluid already available in the body. The latter point is important in deciding whether the function of the kidneys is good enough to permit the use of a mercurial diuretic in a patient with congestive heart failure that has not responded to the usual methods of treatment.

Sodeman and Engelhardt [2] have shown that in normal persons 0.5 cc. of solution of posterior pituitary of twice U. S. P. concentration (10 U. S. P. posterior pituitary units) injected subcutaneously will inhibit the diuresis normally produced by the ingestion of 1,600 cc. of water in fifteen minutes. They have further reported that maximum concentration occurs within the first two hours after the injection of the solution and that 1 cc. of the solution (20 posterior pituitary units) or a previous period of restriction of the intake of fluids or of deprivation of fluids does not further elevate the specific gravity of the urine passed. There is a similar antidiuretic effect in patients with cardiac edema. In normal persons they found that the specific gravity varies from 1.023 to 1.040, whereas in patients with impaired renal function the maximum specific gravity is considerably reduced. In their papers they were more interested in the increase in the specific gravity of the urine passed before and after the injection of the solution of posterior pituitary than in a comparison of their test with a standard concentration test.

It seemed desirable to repeat this work and to compare their test with a standard renal concentration test in a study of a large number of persons with and without impaired renal function.

TECHNIC

The Fishberg [1] renal concentration test was used, in which no fluids are allowed from 5 p. m. of the previous evening until 9 a. m. of the morning of the test. Less than 200 cc. of fluid was allowed with the evening meal, which was high in protein content. The evening meal was eaten about 4:30 p. m. All overnight urine was discarded. Urine specimens were collected at 7, 8, and 9 a. m. and the highest specific gravity recorded.

The test with solution of posterior pituitary was done without special preparation either in the morning or the afternoon. No food or fluid was allowed during the two hour period

1. Fishberg, A. M.: Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 74.

2. Sodeman, W. A., and Engelhardt, H. T.: (*a*) A Renal Concentration Test Employing Post Pituitary Extracts: Response of Normal Subjects, Proc. Soc. Exper. Biol. & Med. **46**: 688-691 (April) 1941; (*b*) A Renal Concentration Test Employing Posterior Pituitary Extract, Am. J. M. Sc. **203**:812-818 (June) 1942.

of the test. The bladder was emptied. A 0.5 cc. dose of solution of posterior pituitary of twice U. S. P. strength (10 U. S. P. posterior pituitary units) or occasionally a similar amount of pitressin was injected subcutaneously. The urine was collected in one and two hours. The higher specific gravity was recorded.

In both tests the specific gravity was measured in a calibrated urinometer and corrections made for albuminuria and temperature. None of the specimens exhibited sugar.

In 11 cases the test with solution of posterior pituitary was compared with a phenolsulfonphthalein test. For the latter the method of Chapman and Halsted [3] was used: The bladder was emptied, 600 cc. of water was ingested and thirty minutes later 1 cc. of phenolsulfonphthalein solution (6 mg.) was injected intravenously. Urine was collected in fifteen minutes and one hour. However, only the result for the fifteen minute sample was recorded, as it was the more significant one.

This comparison with this phenolsulfonphthalein test was included because Goldring, Clarke and Smith [4] showed that at the low concentration in the plasma occurring in the test about 94 per cent of the phenolsulfonphthalein is excreted by tubular secretion and only 6 per cent by glomerular filtration.

RESULTS

A comparison of the maximum values obtained in the test with solution of posterior pituitary and the Fishberg test for 67 subjects is recorded in the tables. The two concentration tests gave similar results. The first test gave slightly higher values in the majority of cases. For the 6 subjects without renal or vascular

TABLE 1.—*Normal Subjects (Persons Without Vascular or Renal Disease)*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
1	18	110/70	1.027	1.026	.....	
2	43	120/80	1.023	1.025	.....	
3	18	122/80	1.026	1.026	.....	
4	25	128/88	1.019	1.027	.....	
5	30	130/90	1.027	1.031	.....	
6	55	100/80	1.020	1.022	.....	

disease (table 1) the values were above 1.022, in keeping with the normal figures published by Sodeman and Engelhardt [2] and Fishberg.[1]

The 43 patients with hypertension or hypertensive heart disease but without renal impairment (table 2) had values above 1.020. Here again there was fairly close similarity with the Fishberg test. The greatest variation was 0.013. In most cases of variation the Fishberg test gave a lower value than the test with solution of posterior pituitary. In 5 cases the Fishberg test gave a result below 1.020 whereas the test with posterior pituitary solution gave a normal result and no other evidence of renal impairment existed.

The 15 patients with definite impairment of renal function (table 4), consisting of 9 with malignant hypertension and 2 with chronic glomerulonephritis, had maximum values for specific gravity below 1.020 in both the Fishberg test and the test with posterior pituitary solution. The comparative results were extremely close, the greatest variation being 0.004.

Only 4 subjects with congestive heart failure were available (table 3). In all 4 the solution of posterior pituitary seemed to give a maximum concentration even in the presence of edema. Although an exact comparison was not available, usually because the edema disappeared too rapidly, my previous experience with the Fish-

3. Chapman, E. M., and Halsted, J. A.: Fractional Phenolsulphonephthalein Test in Bright's Disease, Am. J. M. Sc. **186**:223-232 (Aug.) 1933.

4. Goldring, W.; Clarke, R. W., and Smith, H. W.: Phenol Red Clearance in Normal Man, J. Clin. Investigation **15**:221-228 (March) 1936.

berg test indicates that that test is not reliable in the presence of a reservoir of excess fluid in the body. In the case of subject 50, the specific gravity with the test with posterior pituitary solution was 1.022 and that with Fishberg test 1.023,

TABLE 2.—*Subjects with Hypertension Without Renal Impairment*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
7	44	150/110	1.021	1.020	.....	
8	45	160/110	1.025	1.024	.....	
9	52	200/110	1.020	1.023	.....	
10	51	210/110	1.021	1.025	.....	
11	51	220/120	1.018	1.023	1.024	
12	43	206/136	1.024	1.024	.....	
13	46	170/110	1.018	1.023	.....	
14	50	204/122	1.021	1.023	.....	
15	45	200/130	1.016	1.022	.....	
		150/110	1.024	1.023	.....	5 months later
16	46	190/130	1.024	1.027	1.027	
17	48	178/120	1.020	1.027	.....	
18	51	170/120	1.027	1.022	.....	
				1.025	.....	2 weeks later
19	48	210-250 / 110-160	1.020	1.026	1.024	
20	44	234/160	.....	1.019	.....	
		220/130	1.023	1.021	.....	1 month later
21	48	190/110	1.032	1.030	.....	
22	17	150/ 98	1.029	1.026	.....	
23	44	180/145	1.030	1.022	.....	
24	49	190/130	1.025	1.026	.....	
25	45	190/130	1.022	1.022	.....	
26	46	210/120	1.023	1.023	.....	
27	45	190/100	1.023	1.022	.....	
28	41	190/120	1.026	1.025	.....	
29	49	175/105	1.020	1.020	.....	
30	46	178/110	1.024	1.027	.....	
31	48	140/100	1.023	1.022	.....	
32	48	170/120	1.029	1.024	.....	
33	53	200/110	1.030	1.030	.....	
34	54	155/110	1.024	1.022	.....	
35	55	150/100	.....	1.017	.....	Drank 1 glass of water during test
	55	150/100	1.022	1.028	.....	
36	42	180/120	1.031	1.030	.....	
37	56	180/110	1.022	1.021	.....	
38	47	200/100	1.026	1.028	.....	
39	45	220/140	1.030	1.022	.....	
				1.023	.....	Next day
40	49	155/105	1.017	1.030	.....	
41	53	190-220 / 120/150	1.019	1.023	.....	
42	62	214/124	1.022	1.028	.....	
43	45	160/110	1.026	1.025	.....	
44	48	185/100	1.023	1.023	.....	
45	53	170/110	1.022	1.027	.....	
46	46	150/100	1.023	1.024	.....	
47	50	170/ 90	1.026	1.025	.....	
48	49	205/120	1.021	1.027	.....	
49	51	174/110	1.023	1.028	.....	

TABLE 3.—*Subjects with Congestive Heart Failure*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
50	53	155/105	1.023	1.022	.....	Slight edema
51	51	200/ 30	.....	1.017	.....	Marked edema
			1.015	.....	.....	No edema
52	55	210/ 85	.....	1.019	.....	Marked edema
			1.017	1.019	.....	No edema
53	47	220/120	1.004	1.011	.....	Congestive heart failure with edema during diuresis
			1.011	1.011	.....	No edema

whereas the phenolsulfonphthalein excreted in fifteen minutes was only 15 per cent and the nonprotein nitrogen content of the blood was 50 mg. per hundred cubic centimeters. This patient had been in a state of chronic congestive heart failure for

almost a year and had been treated by administration of digitalis and restriction of fluids. His edema and symptoms were markedly improved by the use of mercurial diuretics. Hence cardiac failure was a prominent factor in the impairment of his renal function.

In the 11 cases in which the test with solution of posterior pituitary was compared with the intravenous phenolsulfonphthalein test (table 5), the results were similar. By the technic used, the normal person excretes an average of 35 per cent

TABLE 4.—*Subjects with Definitely Impaired Renal Function*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
53	47	200/120	1.011	1.011	.....	
54	45	170/110	1.015	1.015	.....	
55	53	240/160	1.015	1.015	.....	Died in uremia 4 weeks later
56	48	240/150	1.023	1.026	.....	
		280/180	1.011	1.015	.....	6 weeks later; died in uremia 3 months later
57	48	180/110	1.014	1.018	1.015	
58	44	260/150	1.010	1.010	.....	
59	48	180/130	1.018	1.017	.....	
60	48	224/170	1.010	1.009	.....	Died in uremia
61	44	200/150	1.015	1.017	.....	
		244/180	.....	1.012	.....	4 weeks later; died in uremia 1 month later
62	50	180/110	1.019	1.016	.....	
63	48	158/110	1.016	1.016	.....	
64	46	140/ 80	1.013	1.014	.....	
65	66	240/150	1.014	1.012	.....	
66	55	166/ 88	1.014	1.012	.....	
67	29	230/165	1.013	1.013	.....	

TABLE 5.—*Comparison of Result of Test with Solution of Pituitary and Intravenous Phenolsulfonphthalein Test*

Subject	Diagnosis	Test with Solution of Posterior Pituitary	Intravenous Injection of Phenolsulfonphthalein (Percentage Excreted After 15 Min.)	Comment
3	Normal	1.026	40	
43	Hypertension	1.025	30	
44	Hypertension	1.023	30	
45	Hypertension	1.027	30	
46	Hypertension	1.024	35	
47	Hypertension	1.025	50	
48	Hypertensive heart disease	1.027	37	
49	Hypertensive heart disease	1.028	40	
50	Hypertensive-arteriosclerotic heart disease	1.022	15	Chronic congestive heart failure
53	Chronic glomerulonephritis with congestive heart failure	1.011	2.5	
66	Hypertension and chronic pyelonephritis	1.012	10	

of the dye in the first fifteen minutes; any amount less than 25 per cent is considered abnormal.

EFFECT OF SOLUTION OF POSTERIOR PITUITARY ON HYPERTENSION AND THE CORONARY ARTERIES

Sodeman and Engelhardt [2b] observed no significant rise in blood pressure with 0.5 cc. of solution of posterior pituitary of twice U. S. P. strength (10 U. S. P. posterior pituitary units). Goodman and Gilman [5] stated that in the normal subject

5. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, pp. 647 and 664.

no rise in blood pressure occurs from the injection of solution of posterior pituitary. I checked the blood pressure in 6 patients with hypertension in whom the readings had ranged from 170 systolic and 120 diastolic to 260 systolic and 170 diastolic, with the patients resting quietly in bed during the procedure. In most of these subjects there was a slight rise in the blood pressure in the first fifteen minutes over the initial resting pressure, but in no case did it go above the usual pressure the patient maintained when he was up and about. None of the patients on whom the test with solution of posterior pituitary was done complained of distressing symptoms. Graybiel and Glendy [6] who injected a dilute solution of pitressin intravenously until distressing abdominal cramps were produced, found only slight changes in pulse rate, blood pressure, cardiac output and metabolic rate in normal persons, in patients with hypertension and in patients with angina pectoris.

Solution of posterior pituitary and pitressin are known to constrict the coronary arteries and this should contraindicate their use in patients with disease of those arteries. My subject 37 had hypertensive arteriosclerotic heart disease with angina class III. Anginal symptoms were produced by slight effort, such as walking up a short flight of stairs. For this patient I used the test with solution of posterior pituitary with extreme caution. He remained in bed for thirty minutes after the injection of 0.5 cc of the solution. He had no discomfort. After he was up and about for fifteen minutes, he felt slight substernal distress and tingling down the left arm. These symptoms promptly disappeared after he used glyceryl trinitrate. Graybiel and Glendy [6] in the aforementioned studies, using an intravenous injection of pitressin, found that anginal pain was not reproduced in 2 patients with severe angina pectoris. They concluded "that pitressin in amounts sufficient to provoke distressing abdominal cramps does not significantly decrease the blood supply to the myocardium in relation to the work of the heart, and that it is safe and practical to give pitressin to patients with coronary heart disease."

COMMENT

This test of renal function promises to be an excellent addition to the standard concentration tests. It seems to be as reliable as the Fishberg test. Its advantages are several. It eliminates the necessity of the patient's cooperating in a prolonged deprivation of fluids. This is important in dealing with an unintelligent or an uncooperative patient such as is often seen in clinic or general hospital practice. It is useful in office practice, saving the patient an extra trip and the necessity of carrying several bottles of urine. Another important advantage is its usefulness in the presence of a reservoir of fluid in the form of ascites or edema, making restriction of fluids impossible. In such a case a prompt estimation of renal function can be obtained. It has been my practice to withold mercurial diuretics from patients in whom there is an inability to concentrate urine to 1.016. If a patient with congestive heart failure has a test showing good concentration of urine (subject 50), even though he has retention of nitrogen, it is safe to use mercurial diuretics.

The mechanism of the antidiuretic action of solution of posterior pituitary is discussed by Goodman and Gilman.[5] The site of action is thought to be the loop of Henle of the renal tubule. This antidiuretic effect is essential for physiologic reabsorption of water by these cells. Solution of posterior pituitary will inhibit water diuresis, but xanthines and mercurial diuretics counteract this antidiuretic action, and one should be careful to omit these drugs before using the posterior pituitary test for renal function.

6. Graybiel, A., and Glendy, R. E.: Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris, Am. Heart J. **21**:481-489 (April) 1941.

Contraindications for this test are pregnancy and coronary heart disease, especially acute myocardial infarction. In the presence of angina pectoris without recent infarction the test should be used with extreme caution.

SUMMARY AND CONCLUSIONS

A renal concentration test using solution of posterior pituitary is described. This test is applicable without the necessity of previously depriving the patient of water and in the presence of edema or ascites. The results obtained for normal subjects, for patients suffering from hypertension without impairment of renal function, and for patients who had impaired renal function compare favorably with the results obtained with the Fishberg and phenolsulfonphthalein tests. The advantages and contraindications are described.

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STUDIES ON THE ACTION OF QUINIDINE IN MAN

I. MEASUREMENT OF THE SPEED AND DURATION OF THE EFFECT FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION

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The value of quinidine in the treatment of certain acute cardiac arrhythmias is well recognized. There are numerous references in the literature about the use of quinidine in treating chronic auricular fibrillation. In this condition, however, conversion to normal sinus rhythm is not urgent, and the dose of quinidine may be gradually increased over a period of days, if necessary, until the desired effect is obtained. In the acute or paroxysmal arrhythmias (auricular tachycardia, auricular fibrillation, ventricular tachycardia, etc.) the abnormal rate and rhythm may cause cardiac pain, intense palpitation, dyspnea, faintness, vomiting, pulmonary edema, collapse and even death. Prompt treatment may be essential. Proper management of such conditions requires accurate knowledge of the speed and duration of action of the therapeutic agents employed. Little exact information is available, however, concerning the factors which determine the optimum methods for employing quinidine under such conditions.

The purpose of this communication is to present measurements of the speed and duration of action of cinchona derivatives in subjects with normal cardiac rhythm. Different preparations of quinidine and quinine have been used; the dose was varied, and the drugs were administered by mouth and also by intramuscular injection. The effects of quinidine and quinine on the heart were studied by means of changes in the electrocardiogram induced by these drugs.

REVIEW OF THE LITERATURE

The speed of onset and the duration of action of quinidine have been studied by determining the concentration in the blood stream, the concentration in the cardiac musculature, the rate of excretion in the urine, the changes in the heart rate observed in patients with various arrhythmias and the changes produced in the electrocardiogram. The results of these studies are confusing.

Laboratory Studies.—In the blood stream of man or laboratory animals very little of the drug can be detected five to ten minutes after the oral or intravenous administration of a single dose of quinidine [1] or quinine.[2] In the myocardial tissue of dogs the maximum concentration is reached within one-half to one hour after

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1. (*a*) Weisman, S. A.: Further Studies in the Use of Quinidine in the Treatment of Cardiac Irregularities, Minnesota Med. **22**:385, 1939. (*b*) Weiss, S., and Hatcher, R. A.: Studies on Quinidin, J. Pharmacol. & Exper. Therap. **30**:335, 1927.

2. (*a*) Hatcher, R. A., and Gold, H.: Studies on Quinin, J. Pharmacol. & Exper. Therap. **30**:347, 1927. (*b*) Hatcher, R. A., and Weiss, S.: Studies on Quinin, ibid. **29**:279, 1926.

oral administration, while four to seven hours later the drug can no longer be found.[3] In the urine the alkaloid appears within two to three hours after oral administration and traces can be detected up to twelve to twenty-four hours.[4] If a cinchona derivative is administered in divided doses, the maximum concentration is found in the blood [10a] or myocardium [3] about one to two hours after the last dose. Under these conditions a larger total amount is excreted in the urine [5] and a smaller amount is found in the myocardium [3] than when the same total amount is given as one single dose.

Clinical Studies.—When a cinchona derivative is given to a patient with auricular fibrillation or flutter,[6] a slowing of the auricular rate and an increase in the ventricular rate have been observed. These effects become evident about one-half hour after administration of a single dose by mouth, reach a maximum in two to three hours and begin to decrease about one hour later. They are still present eight hours after administration of the drug but are not apparent in twenty-four to thirty hours. When quinidine is given intravenously, the maximum slowing of the auricles occurs within ten minutes and persists for ten to fifteen minutes, after which the auricular rate increases slowly, returning to the original level after five hours in most cases.[7]

Similar information is obtained by observation of the ventricular rate during quinidine therapy of ventricular tachycardia. Scott [8] reported on 1 patient in whom such paroxysms could be terminated invariably one-half to one hour after the oral administration of 0.4 Gm. of quinidine sulfate. Riseman and Linenthal,[9] in treating a patient with ventricular tachycardia of eight and one-half days' duration, observed that the effect of each dose (quinidine sulfate by mouth or quinine dihydrochloride intramuscularly) became evident in one-half to one hour and reached its maximum within two hours, following which the effect decreased so that after approximately ten hours it was negligible.

Wilson and Wishart [7] found that when quinidine was given intravenously to patients with auricular fibrillation the response occurred within ten minutes and the magnitude of effect was about twice as great as when given orally. Because the toxic effects were so great, these investigators concluded that intravenous administration "promises comparatively little from the standpoint of practical therapeutics." Hepburn and Rykert [10] treated 9 patients with ventricular tachycardia

3. Weisman, S. A.: Studies on the Time Required for the Elimination of Quinidine from the Heart and Other Organs, Am. Heart J. **20**:21, 1940.

4. (*a*) Lewis, T.; Drury, A. N.; Wedd, A. M., and Iliescu, C. C.: Observation upon the Action of Certain Drugs upon Fibrillation of the Auricles, Heart **9**:207, 1922. (*b*) Lewis, T.: The Value of Quinidine in Cases of Auricular Fibrillation and Methods of Studying the Clinical Reaction, Am. J. M. Sc. **163**:781, 1922. (*c*) Wedd, A. M., and Hubbard, R. S.: Notes on Dosage and Excretion of Quinidine Sulfate, Clifton M. Bull. **15**:69, 1929.

5. Wiechmann, E.: Ueber die Ausschiedung des Chinidins im Harn, Ztschr. f. d. ges. exper. Med. **7**:155, 1919.

6. (*a*) Wedd, A. M.: Notes on the Action of Certain Drugs in Clinical Flutter, Heart **11**:87, 1924. (*b*) Scott, R. W.: Clinical Observations on Quinidine, J. Pharmacol. & Exper. Therap. **19**:264, 1922. (c) Lewis, Drury, Wedd and Iliescu.[4a] Lewis.[4b]

7. Wilson, F. N., and Wishart, S. W.: The Effects Produced by the Intravenous Injection of Quinidin and Other Drugs upon the Mechanism of the Heart Beat, Tr. A. Am. Physicians **41**:55, 1926.

8. Scott, R. W.: Observations of a Case of Ventricular Tachycardia with Retrograde Conduction, Heart **9**:297, 1922.

9. Riseman, J. E. F., and Linenthal, H.: Paroxysmal Ventricular Tachycardia, Am. Heart J. **22**:219, 1941.

10. Hepburn, J., and Rykert, H. E.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, Am. Heart J. **14**:620, 1937.

by administering a 10 to 12 per cent solution of quinidine sulfate in 5 per cent dextrose solution at a rate of 100 to 120 cc. per hour. The average dose was slightly less than 20 grains (1.3 Gm.).

The conditions under which such clinical studies were carried out do not lend themselves to accurate or prolonged study of the speed and duration of action of the drug used. As a result there is no uniformity of opinion as to the optimum methods of their use.

Choice of Preparation.—Frey [11] and later Lewis, Drury, Wedd and Iliescu [4a] found that quinidine was more effective than quinine in the treatment of auricular fibrillation. Grant and Iliescu [12] found quinidine more effective than cinchonidine, cinchonine or quinine.

Wiechmann [5] concluded that the sulfate was more readily absorbed than the alkaloid, for he found greater urinary excretion following administration of the salt. Lewis and his co-workers [4a] found no difference in the response to the sulfate, the bisulfate and the dihydrochloride of quinidine given orally and suggested that all are converted to the hydrochloride in the stomach.

The choice of preparation at present is limited. Practically all the drug is imported, the American pharmaceutic houses acting as distributing agents. The alkaloid, the sulfate and the hydrochloride are available, the relatively insoluble sulfate being most generally used. The more soluble dihydrochloride and citrate, which might be more suitable for injection, are not available. The formula for the injectable quinidine hydrochloride with urea and antipyrine [13] used in the present study was suggested by the Cinchona Institute. So far as is known, it has not been used previously, but it is similar to a preparation of quinine hydrochloride with urea and antipyrine which has been used in treating certain infectious diseases.[14]

Electrocardiographic Studies.—Electrocardiographic changes have been observed following the administration of quinine [15] and quinidine.[16] The most consistent

11. Frey, W.: Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl. klin. Wchnschr. **55**:450, 1918.

12. Grant, R. T., and Iliescu, C. C.: Comparison on the Action of Quinidine with Other Cinchona Alkaloids in Auricular Fibrillation, Heart **9**:289, 1922.

13. Quinidine hydrochloride 15 Gm., urea 20 Gm., antipyrine 15 Gm. and distilled water to make 100 cc.

14. (*a*) Zuelzer, G.: Zur Schlarlachfrage, Berl. klin. Wchnschr. **56**:1131, 1919. (*b*) Cahn-Bronner, C. E.: Die Behandlung der Lungentzündung mit subkutanen Chinininjektionen, Ztschr. f. klin. Med. **87**:292, 1919. (*c*) Schwarze: Ueber lokale Behandlung des Keuchhustens, Fortschr. d. Med. **44**:1014, 1926.

15. (*a*) Hecht, A. F., and Matkow, J.: Intravenöse Chinininjektionen bei Malariakranken, Wien. klin. Wchnschr. **30**:169, 1917. (*b*) Hecht, A. F., and Rothberger, C. J.: Experimentelle Beiträge zur Kenntnis der Chininwirkung bei Herzflimmern, Ztschr. f. d. ges. Med. **7**:134, 1919. (*c*) Singer, R., and Winterberg, H.: Chinin als Herz- und Gefässmittel, Wien. Arch. f. inn. Med. **3**:329, 1922. (*d*) Miki, Y.: Experimentelle und klinische Untersuchungen über die Dauer des K-Ekg (Kammer-Elektrokardiogramms), Ztschr. f. d. ges. exper. Med. **27**:323, 1922. (*e*) Hughes, T. A.: Effect of Intravenous Injections of Quinine on Electrocardiogram in Man, Indian J. M. Research **19**:113, 1931. (*f*) Aschenbrenner, R.: Ueber die Beeinflussung der Herzstromkurve und andere Nebenwirkungen bei der Chinin-Therapie, Klin. Wchnschr. **16**:1750, 1937.

16. (*a*) Schott, E.: Zur Frage der Chinidintherapie, Deutsches Arch. f. klin. Med. **134**: 208, 1920. (*b*) Cohn, A. E., and Levy, R. L.: Experimental Studies on the Pharmacology of Quinidine, Proc. Soc. Exper. Biol. & Med. **8**:283, 1920-1921. (*c*) Korns, H. M.: An Experimental and Clinical Study of Quinidine Sulfate: I. Experimental, Arch. Int. Med. **31**:15 (Jan.) 1923. (*d*) Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1933. (*e*) Maher, C. C.; Sullivan, C. P., and Scheribel, C. P.: Effect upon Electrocardiogram of Patients with Regular Rhythm of Quinidine Sulfate, Am. J.

findings after the giving of therapeutic doses to human beings have been a flattening, broadening and occasional notching of the T wave and an increase in the duration of the QT interval (the duration of electrical systole of the ventricle, measured from the beginning of the QRS complex to the end of the T wave).

Maher, Sullivan and Scheribel [16e] have utilized the qualitative changes in the contour of the T wave to determine the speed and duration of action of quinidine. With intravenous administration of 3 grains (0.2 Gm.) of quinidine sulfate in 20 cc. of distilled water, these changes in the T wave were observed within a few minutes and persisted for at least three hours. After oral administration (quinidine sulfate, 10 grains [0.65 Gm.] three times a day or 15 grains [1 Gm.] four times a day, for five to nineteen days) the changes in the T wave were observed to begin in twelve to seventy-two hours and to disappear after several days.

METHODS AND MATERIAL

Sixteen hospitalized subjects with normal sinus rhythm were used in these studies: One had angina pectoris, 2 had had paroxysmal arrhythmias, 2 had hypertension and 11 had no evidence of cardiac disease; 1 was known to have achlorhydria. Eleven were men, and 5 were women. The ages varied from 17 to 68 years; 10 were over 45. Standard four lead electrocardiograms showed no evidence of coronary artery disease.

All studies were carried out in a uniform manner. A control four lead electrocardiogram was obtained. The medication was then administered and electrocardiograms were made every fifteen minutes for the first hour and then at less frequent intervals for a total of eight to fifteen dours. An additional tracing was taken twenty-four hours after the administration of the drug. The patients remained in bed except for lavatory privileges while the studies were carried out and were recumbent for at least five minutes before each tracing was obtained. No attempt was made to control the diet. Use of all drugs which might have some effect on the heart or electrocardiogram were omitted during the period of study except those being investigated. At least forty-eight hours was allowed to elapse before these studies were repeated on any person.

The effect of the following medication was studied: quinidine sulfate, single doses by mouth of 3, 5, 9, 10 or 15 grains; quinine sulfate, 5 grains by mouth; injectable quinidine (quinidine hydrochloride with urea and antipyrine), 5 grains intramuscularly; quinidine sulfate, repeated doses by mouth of 3 grains at intervals of one, two, four or eight hours or of 5 grains every four hours for two doses; quinidine hydrochloride with urea and antipyrine, intramuscular injections every two hours for five doses.

A total of 68 tests were performed. In 36 tests the three conventional leads and a precordial lead (IVR) were used (452 four lead tracings). In the remaining 32 tests lead II only was used (742 one lead tracings). In determining the duration of the QT interval seven to ten consecutive complexes were estimated to 0.01 second and the average was obtained. The variation in duration of consecutive QT intervals was 0.01 second. When the tests were repeated on different days the average of the duration of seven to ten consecutive complexes differed by less than 0.01 second.

RESULTS

In all 68 tests the effect of the cinchona derivatives was evidenced by a prolongation of the QT interval. In 61 tests the effect of medication was also evidenced by striking qualitative changes in the T wave. These did not lend themselves to a quantitative estimation of the frequency, degree, duration or time of onset of the quinidine effect; furthermore, they appeared later and disappeared earlier than the change in the duration of QT. These changes were observed in all four leads. The qualitative changes in the T waves were most striking in lead IVR (chart 1), but the termination of the T wave in this lead and also in lead III was not sufficiently

M. Sc. **187**:23, 1934. (*f*) Aschenbrenner, R.: Ueber das Digitalis-Elektrocardiogram, Klin. Wchnschr. **15**:1039, 1936. (*g*) Landau, N.: Ueber die Verlängerung der Systole bei Tetanie und ihre Beeinflussung durch verschiedene Pharmaca, ibid. **17**:93, 1938. (*h*) Freedberg, A. S.; Riseman, J. E. F., and Spiegl, I.: Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris, Am. Heart J. **22**:494, 1941.

definite to make accurate measurements of the QT intervals possible. The results in leads I and II were essentially similar; for simplicity, only the results of lead II are presented.

In general, the degree of electrocardiographic response to a single dose of one of the cinchona derivatives followed a characteristic curve (chart 2). The effect became evident shortly after the administration of the drug and increased rapidly, reaching a maximum in one and one-half to three hours. Thereafter, the degree of effect was maintained at a slightly lower level for approximately three to five hours,

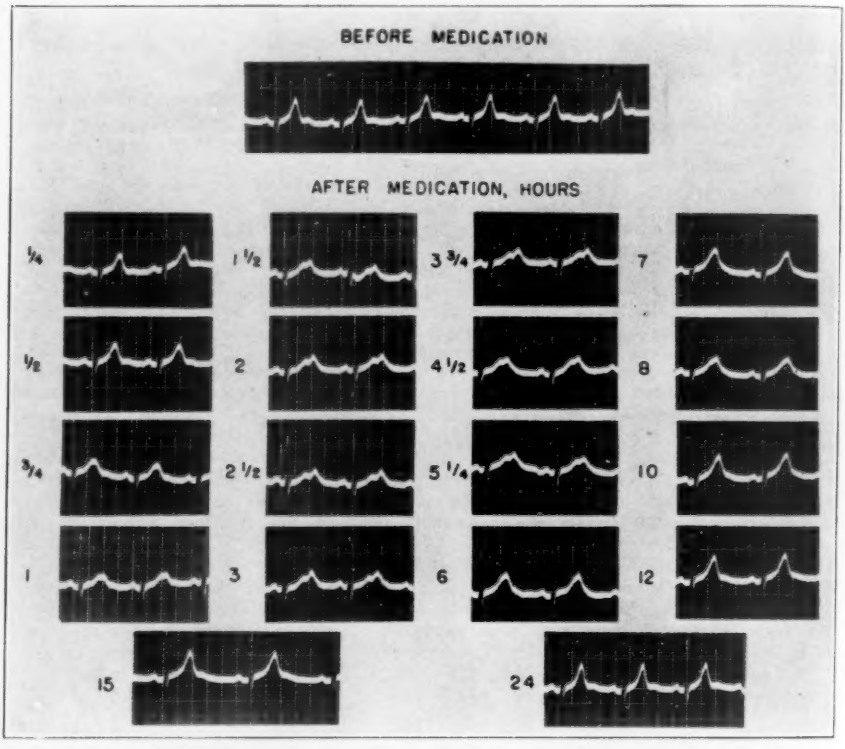

Fig. 1.—Typical prolongation of the QT internal and flattening of the T waves in the electrocardiogram following the administration of quinidine (patient N. J., 15 grains of quinidine sulfate by mouth; lead IVR).

after which it decreased, at first rapidly and then more slowly, and was no longer evident in twenty-four hours.

The Effect of Single Doses.—The Comparative Effects of Different Amounts of Quinidine Sulfate Given Orally in Single Doses: These were studied in 14 patients. Eleven patients received 3 grains, 10 received 5 grains (0.3 Gm.), 3 received 9 grains (0.6 Gm.), 6 received 10 grains and 6 received 15 grains. The comparative effects of these different doses is best shown by the results obtained in 6 patients, each of whom received 3, 5, 10 and 15 grains on different days (chart 3).

In general, as the dose was increased the degree and duration of the effect were also increased and the effect became evident more rapidly. The variation of response to single doses in the subjects studied is shown in table 1. After the administration of 10 or 15 grains, 4 of the 6 patients showed slight but definite prolongation of the QT interval within fifteen minutes; only 1 patient showed a similar response to

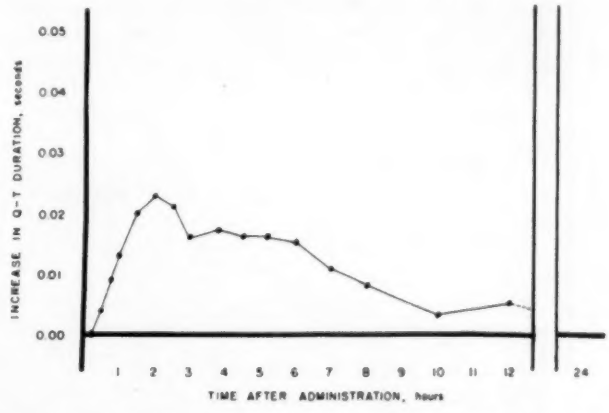

Fig. 2.—Electrocardiographic response to a single 3 grain dose of quinidine sulfate given by mouth (average of results obtained in 11 patients).

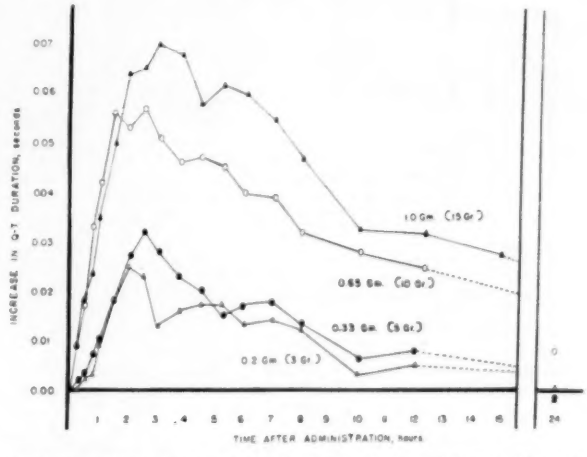

Fig. 3.—The comparative effects of single doses of 3, 5, 10 and 15 grains of quinidine sulfate given by mouth (average of results obtained in 6 patients).

5 grains, while no patient showed so rapid a response to 3 grains. The maximum effect was reached in one and one-half to three and three-fourths hours, irrespective of the amount of drug administered.

One of the 10 patients who received a single 5 grain dose of quinidine sulfate had pernicious anemia and complete achlorhydria. The effect in this patient was similar to that observed in the remaining 9 patients.

TABLE 1.—*Variation in Response to Single Doses of Quinidine Following Oral and Intramuscular Administration*

Patient	Onset of Recognizable Effect (Hours After Administration)					Maximum Effect (Hours After Administration)					Disappearance of Effect (Hours After Administration)				
	Oral				I. M.	Oral				I. M.	Oral				I. M.
	3 Gr.	5 Gr.	10 Gr.	15 Gr.	5 Gr.	3 Gr.	5 Gr.	10 Gr.	15 Gr.	5 Gr.	3 Gr.	5 Gr.	10 Gr.	15 Gr.	5 Gr.
I. L.	1	¼	¼	¼	¼	1½	1½-2	1-2	1½-2	1½-4½	8-10	8-10	>8	>15	>10
B. K.	¾	1	¼	¾	¼	2-2½	2-3	2-3	2½-3	1½-2	8-10	8-10	>12	>15	7-8
I. S.	1½	1½	¼	1	¼	2½	2-3	2½	3	1½	8-10	>12	>12	>15	>10
H. J.	1	1½	¾	¼	¼	2½	2½-3¾	2½-3¾	3-3¾	1½-2	8-10	10-12	8-10	>15	8-10
E. H.	1	½	¾	¼	¼	2	2½	2½	2-3¾	1½-2½	>12	>12	>12	>15	7-8
E. B.	½	1½	¼	½	¼	1½-2½	2¼-5¾	1½-2½	2½-3¾	1½	>12	>12	>12	>15	7-8
H. R.	.1	..	..	..	..	3	..	....	....	....	7	....	....	....	....
J. Z.	¾	..	..	..	..	2-3	..	....	....	....	6	....	....	....	....
M. T.	½	..	..	..	..	1½	..	....	....	....	6	....	....	....	....
S. G.	½	..	..	..	..	1½	..	....	....	....	8	....	....	....	....
G. B.	½	..	..	..	..	1-2	..	....	....	....	8	....	....	....	....
J. W.	..	½	..	..	..	..	2-2½	....	....	....	....	>10	....	....	....
C. G.	..	¼	..	..	..	..	1½	....	....	....	....	>10	....	....	....
M. S.	..	½	..	..	..	..	1½	....	....	....	....	8-10	....	....	....
M. R.	..	½	..	..	..	..	2-3	....	....	....	....	>8	....	....	....
Average	¾	¾	½	½	¼	2	2½	2½	3	2	8-10	8-12	8->12	>15	7-10

The Comparative Effects of Oral and Intramuscular Administration of Quinidine: Six of the patients who were given single 5 grain doses of quinidine sulfate by mouth subsequently received 5 grains of injectable quinidine (quinidine hydrochloride with urea and antipyrine) by the intramuscular route (chart 4). All patients showed a definite response within fifteen minutes; tracings for 2 patients were obtained five minutes after the injection and showed the characteristic effect. In comparison, 4 of these 6 patients after a similar dose by mouth failed to show electrocardiographic changes until one to one and one-half hours. The maximum effect of the intramuscular injection was obtained in one and one-half hours in all

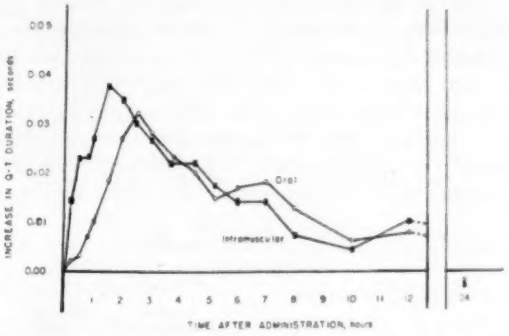

Fig. 4.—The comparative effects of oral and intramuscular administration of quinidine (average of results obtained in 6 patients).

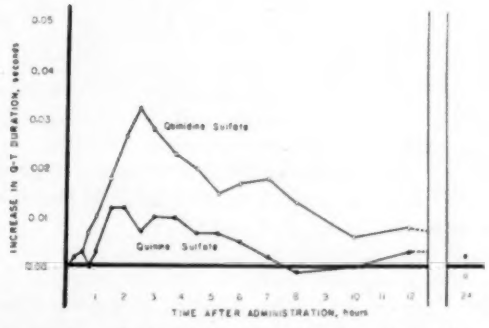

Fig. 5.—The comparative effects of quinidine sulfate and quinine sulfate (average of results obtained in 6 patients).

6 patients, whereas when the drug was given orally 5 failed to show the maximum effect until two to two and one-half hours. In 4 patients the maximum effect following intramuscular injection was significantly greater than that following oral administration. The duration of the effect was approximately the same when the drug was given by the two different routes.

Comparison of Quinidine Sulfate and Quinine Sulfate: The same 6 patients were given 5 grain doses of quinine sulfate by mouth (chart 5). Although similar electrocardiographic changes were observed in response to quinine sulfate, the magnitude and duration of these changes were much less than those following administration of quinidine sulfate.

The Effect of Repeated Doses.—The Effect of Repeated Doses of Quinidine Sulfate Given Orally: This was studied in 9 patients (table 2). The effect of medication administered repeatedly in this manner was compared with the response to single doses of 3 or 5 grains and also with the response to single doses equal in magnitude to the total amount given, namely, 9, 10 and 15 grains.

Comparison of the Effects of Single and Repeated Three and Five Grain Doses: In general, the effect of repeated doses could be predicted from the response to a single dose. The effect of repeated doses at any time was approximately the sum of the effects of the individual doses administered up to that moment as known from previous curves of the responses to single doses. The method of predicting the combined effects from the individual curves is shown in chart 6.

When medication was administered at hourly intervals, the patient received successive doses before the maximum effect of the preceding dose had been obtained. As a result the effect increased progressively, reaching a maximum two to four hours after the first dose (chart 7 *A*). The effect did not disappear entirely twelve hours after the first dose was given (ten hours after the third dose).

When medication was administered at two hour intervals, the patients received successive doses shortly after the maximum effect of the preceding dose had been

TABLE 2.—*Dosage Used for Study of Effect of Repeated Oral Administration of Quinidine Sulfate*

Size of Dose, Grains	Hours Between Administration	Number of Doses	Number of Patients Studied
3	1	3	3
5	1	5	2
3	2	3	3
3	2	5	2
3	4	3	3
3	8	4	2
5	4	2	3

reached. As a result it was usually possible to observe the maximum effect of each dose before the succeeding dose was administered (chart 8). When medication was administered at two hour intervals instead of at hourly intervals, the maximum prolongation of the QT interval began later and persisted longer but was approximately of the same magnitude (chart 7 *A* and *B*).

When medication was administered at four hour intervals, the effect of the preceding dose had decreased sufficiently so that the response to each individual dose was even more apparent than when the drug was given at two hour intervals (chart 7 *B*, *C* and *D* and chart 8). Here again the maximum prolongation of the QT interval was of approximately the same magnitude as when the same dose was given at more frequent intervals.

When medication was administered at eight hour intervals, the effect of the preceding dose had practically disappeared. As a result the response to the fourth dose administered was essentially the same as the response to the first dose in speed of onset, magnitude and duration (chart 9).

When medication was repeated five times (at either one or two hour intervals), the effects of the fourth and fifth doses were somewhat less than the effects of the individual first three doses.

Comparison of the Effect of Nine, Ten and Fifteen Grains of Quinidine Sulfate Given in Single and Divided Doses: When 9 or 10 grains was given in divided doses (3 or 5 grains given at one, two or four hour intervals for two or three

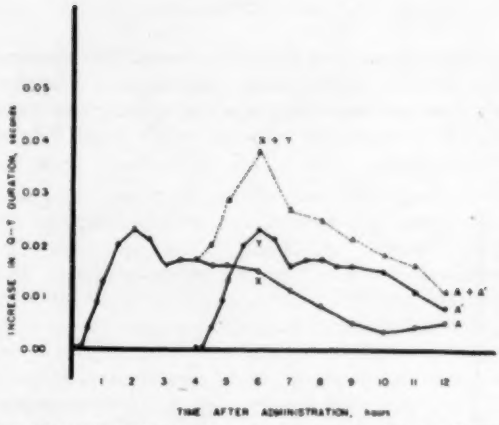

Fig. 6.—Method of calculating response to repeated doses. Curve *A* indicates response to a single 3 grain dose of quinidine sulfate given by mouth (average of results obtained in 11 patients). Curve *A'*, similar results which would have been obtained if a previous dose had not been given. Curve *AA'*, predicted effect of repeated doses obtained by the addition of curves *A* and *A'*.

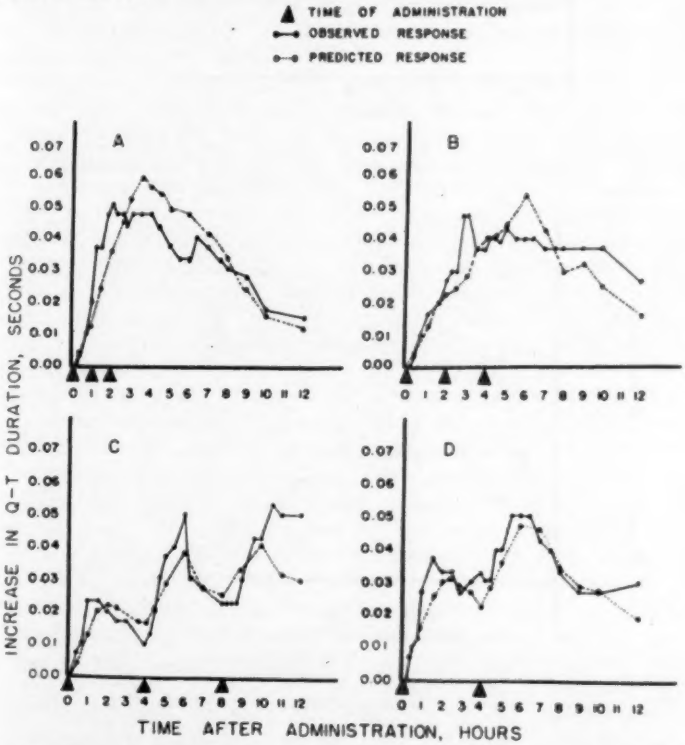

Fig. 7.—Comparison of the observed and the predicted response to repeated oral doses of quinidine sulfate: *A*, 3 grains at hourly intervals for three doses; *B*, 3 grains at two hour intervals for three doses; *C*, 3 grains at four hour intervals for three doses; *D*, 5 grains at four hour intervals for two doses. The observed response is an average of results obtained in 3 patients; the predicted response is based on an average of results obtained in 11 patients (*A*, *B* and *C*) and 9 patients (*D*).

doses), the maximum prolongation of the QT interval was essentially the same as when the total amount was given as one single dose. When 15 grains was given in divided doses, the maximum effect was slightly less than that following the single dose. In each case, however, the response to the single dose appeared more rapidly and was less prolonged.

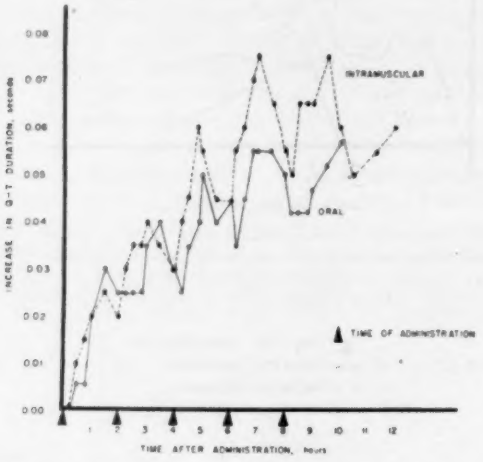

Fig. 8.—Comparison of the effects of repeated doses of oral and intramuscular preparations of quinidine, 3 grains given at two hour intervals for five doses (average of results obtained in 2 patients).

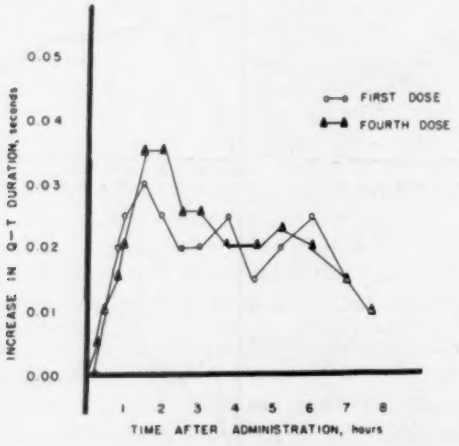

Fig. 9.—The effect of 3 grains of quinidine sulfate administered by mouth at eight hour intervals. The electrocardiographic response to the first dose is compared to that of the fourth dose, which was given twenty-four hours later (average of results in 2 patients).

Comparison of the Effect of Repeated Doses of Oral and Intramuscular Preparations of Quinidine: Two patients received five 3 grain doses of each preparation given at two hour intervals. The response to each intramuscular injection appeared within fifteen minutes, whereas the response to each oral administration did not appear for one-half to three-fourths hour. In most instances greater prolongation

of the QT interval followed the administration of the drug by the intramuscular route. Regardless of the route of administration, when the drug was given at two hour intervals, it was usually possible to observe the maximum effect of the preceding dose.

COMMENT

It is evident from the literature that the magnitude of response to quinidine varies with the amount administered and that if repeated doses are given at appropriate intervals evidence of cumulative action becomes apparent. The concentration of cinchona derivatives in the blood, myocardium or urine after administration of the drug is of considerable interest, but these studies give little direct information concerning the degree and time of the therapeutic action in man.

More direct information of the clinical response is obtained from studies of the effect in various arrhythmias. As a result of such information many different methods of administering quinidine have been proposed. The drug has been prescribed in increasing or identical doses at periods varying from once an hour to once every five or six hours.[17] These methods have proved of value in treating chronic auricular fibrillation and in the prophylactic treatment of paroxysmal arrhythmias. They are obviously unsuited for the treatment of acute episodes for which rapid control of the rhythm may be necessary and for which it is advisable to evaluate the effect of previously administered medication before additional doses are given with the least possible delay.

Although the electrocardiographic changes following administration of quinidine have been previously recognized, few attempts have been made to utilize this knowledge for studying the effect of cinchona derivatives on the human heart. The results obtained in the present study show that although qualitative changes in the T wave as described by Maher, Sullivan and Scheribel[16e] may be striking, they vary in different patients and in the same patient at different times and may be absent or not sufficiently definite to make accurate measurement possible.

The prolongation of the QT interval following the administration of cinchona drugs in our experience is a constant factor which varies but little in different patients. This change is measurable and increases as the amount of drug is increased. It is probably closely related to the mechanism responsible for the conversion of abnormal to normal rhythm, for the QT interval (duration of electrical systole) is related to the refractory period of the ventricular muscle. In the treatment of ventricular tachycardia, for example, the quinidine effect is evidenced by a prolongation of the duration of each ventricular complex.[9]

The results of the present studies are in accord with the observations of the effect of quinidine made in the clinical treatment of arrhythmias. The present studies are more complete, however, for the response was observed for longer periods and under conditions which lent themselves to more careful quantitative measurement. That the results observed in normal subjects are applicable to patients with abnormal cardiac rhythms has been shown by clinical experience.[18]

The present studies show that the maximum effect of any single dose of quinidine or one of its derivatives is usually attained in one and one-half to two

17 (*a*) Weisman, S. A.: The Ambulatory Treatment of Auricular Fibrillation with Quinidine: A Five-Year Follow-Up Study, Minnesota Med. **19**:349, 1936. (*b*) Kerr, W. J.: Use of Quinidine in Cardiac Irregularities, in Stroud, W. D.: The Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940, p. 1195. (*c*) Weiss, S.: The Treatment of Vertigo and Syncope, J. A. M. A. **118**:529 (Feb. 14) 1942. (*d*) Weisman (footnotes 1 *a* and 3). Lewis, Drury, Wedd and Iliescu.[4a]

18. Sturnick, M.; Riseman, J. E. F., and Sagall, E. L.: Studies on the Action of Quinidine in Man: II. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias, J. A. M. A. **121**:921 (March 20) 1943.

and one-half hours after administration. Obviously, therefore, *if the desired effect is not obtained within two hours additional quinidine will usually be necessary and delay in administering such medication is inadvisable.*

More rapid and more striking effects can be obtained by administering the drug at more frequent intervals, for example, every hour. Under such conditions, the maximum effect of preceding doses will not have been obtained, and it is possible that toxic effects of quinidine may occur several hours after the drug is withdrawn. This method, however, is of value if the danger from continuation of the abnormal rhythm is greater than the danger from overquinidinization.

It is probable that the toxic effects of quinidine have been overemphasized in the past. The untoward reactions may be grouped under four headings:

1. Hypersensitivity. This includes collapse with cardiorespiratory failure, etc. Such symptoms are likely to occur soon after the dose is administered and even after small doses. In the absence of a clearcut history of hypersensitivity to cinchona derivatives it is unlikely that such unfortunate complications can be avoided. In our experience with patients with angina pectoris [19] cutaneous manifestations of an allergic nature are likely to occur if quinidine has been administered previously; untoward reactions to quinidine, however, are uncommon. The infrequency of more serious reactions may possibly be related to the fact that quinine is less generally used as a therapeutic agent at present. The rarity of such reactions makes the danger of quinidine hypersensitivity much less than the danger of continuation of an acute arrhythmia in most instances.

2. Reactions following conversion to normal rhythm. These include embolic phenomena following resumption of normal auricular contractions in auricular fibrillation with dislodgment of mural thrombi. Sudden collapse with vomiting and marked fall in blood pressure following conversion to normal rhythm, even in the absence of embolic phenomena, is seen occasionally. Here again the reaction is not necessarily related to the size of the dose, and the possible danger from such effects must be weighed against the dangers of continuation of the abnormal rhythm.

3. Reactions following overdosage. These include vomiting, epigastric distress, diarrhea, fever and tinnitis. In most instances they can be avoided by giving no more quinidine than necessary to control the rate and rhythm.

4. Precipitation of ventricular tachycardia or fibrillation. Seven instances have been reported in the literature.[20] Five occurred during the treatment of auricular fibrillation, and the reaction was probably due to a slowing of the auricular rate without adequate auriculoventricular block. In the remaining 2 cases [20d] there were frequent attacks of ventricular fibrillation which occurred spontaneously or could be precipitated by several drugs, including quinidine given intravenously.

The advantages of intramuscular administration for the treatment of acute arrhythmias are obvious. The response to parenteral injection is prompt and quantitative. Furthermore, absorption is assured when the drug is administered by injection, while when given by mouth it may be vomited or may remain in the stomach mixed with undigested food and not be available to cardiac tissues. To

19 (*a*) Riseman, J. E. F., and Brown, M. G.: Medicinal Treatment of Angina Pectoris. Arch. Int. Med. **60**:100 (July) 1937. (*b*) Freedberg, Riseman and Spiegl.[16h]

20. (*a*) Levy, R. L.: The Clinical Toxicology of Quinidin, J. A. M. A. **78**:1919 (Sept. 30) 1922. (*b*) Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy, Heart **9**:269, 1922. (*c*) Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, Am. Heart J. **4**:559, 1929. (*d*) Schwartz, S. P., and Jezer, A.: The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, ibid. **9**:792, 1934.

the best of our knowledge the preparation used in this study for intramuscular injection has not been used heretofore in the treatment of cardiac arrhythmias. This preparation is not yet available commercially, but it can be prepared easily from drugs available now. Medication in such form can be carried in the physician's bag for emergency use and makes it possible to administer adequate quinidine dosage in small volumes. Administration by the intramuscular route is safe and not painful. Its use in the treatment of acute arrhythmias is being reported in a separate communication.[18]

SUMMARY AND CONCLUSIONS

After the administration of a cinchona derivative to a human being the electrocardiogram uniformly shows an increase in the time from the beginning of the Q to the end of the T wave. In the present study this index of the effect on the human heart was used to measure the speed and duration of action of quinidine and quinine administered to human beings either orally or by intramuscular injection.

The effect became evident shortly after the administration of a single dose by mouth, reached a maximum in one and one-half to three hours, was then maintained at a slightly lower degree for three to five hours, after which it decreased, at first rapidly then more slowly, and was no longer evident in twenty-four hours.

Quinine was much less effective than quinidine.

Larger doses of quinidine sulfate did not change the time of the maximum response, although the effect became evident sooner and was more prolonged.

The response to intramuscular administration of injectable quinidine[13] (a solution of quinidine hydrochloride with urea and antipyrine) was much more prompt (within fifteen minutes) and the magnitude of effect was slightly greater, but the duration of effect was approximately the same as when an equivalent dose was given by mouth.

When doses are given repeatedly either orally or intramuscularly, the response at any moment is essentially the sum of the separate effects of the individual doses acting at that moment.

These results indicate that in the treatment of acute arrhythmias the administration of quinidine should be repeated at intervals of two to two and one-half hours. This permits observation of the maximum effect of the preceding dose before continuation of therapy with minimum loss of time.

If more rapid control of the rate is required, administration of the drug may be repeated at intervals of one hour until the desired degree of slowing is attained, after which therapy can be continued at intervals of two to two and one-half hours.

In the treatment of acute arrhythmias, intramuscular administration should provide more constant and earlier response and eliminate the uncertainties and irregular absorption of oral medication. Intravenous administration is unnecessary and unwise.

Mr. Harry Brass, Ph.G., assisted us in preparing the injectable quinidine.

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EFFECTS OF VITAMIN A DEPLETION IN YOUNG ADULTS

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The lack of agreement as to what constitutes subclinical vitamin A deficiency and the uncertainty existing as to the order of the occurrence of the supposed early signs in relation to one another prompted the undertaking of this study. The various suggested symptoms of early avitaminosis A include: defective dark adaptation, macroscopic and microscopic changes in the skin and conjunctivas, changes in the total and differential white blood counts and decreased vitamin A content of the blood. Each of these factors has been investigated individually; there have been studies in which only two or three of the aforementioned signs have been followed in any one subject, the most usual method being to observe dark adaptation and one other sign. It was believed, therefore, that careful observations for all of the suggested subclinical signs of progressive vitamin A deficiency in the same subjects on a vitamin A–low diet would at least clarify the order of their appearance.

In conjunction with this investigation a study on animals [1] in which the hepatic stores of vitamin A of rats on a vitamin A–free diet were correlated with some of these same signs was also undertaken with the hope that it might furnish data to help interpret the findings in human subjects.

EXPERIMENTAL METHODS

Six university students, 4 women and 2 men, ranging in age from 20 to 24 years, were placed on a vitamin A–low diet [2] for thirty-one and twenty weeks respectively. The diet contained from 67 to 100 U. S. P. units of vitamin A per day. The foods furnishing any vitamin A or source thereof were weighed and consumed in equal amounts by all, with the exception of meat, of which the men received one and one-half times as much as the women. All other foods were allowed as desired. The flour used for cooking and baking was enriched. No concentrates were added to the diet, since it furnished adequate amounts of the other dietary constituents for a sedentary adult, according to the standards set up by the National Research Council. One of the women (subject S. B.) acted as the control and received 10,000 U. S. P. units of vitamin A daily in the form of halibut liver oil capsules [3] in addition to the vitamin A–low diet.

The method employed for detecting the effects of vitamin A deficiency included measurements of dark adaptation and visual fields, of the vitamin A and carotene content of the blood and of histologic changes in the skin and conjunctivas. Total white blood cell counts and differential counts were also included. Most of these analyses were made prior to the experimental regimen, so that the normal base line for each subject could be determined. Dark adaptation was measured on three instruments. Two tests a week were given each subject, both on the biophotometer and on the Hecht adaptometer; during the last two or three weeks the subjects were tested on the regenometer,[4] which differs from the preceding two instruments

From the Department of Home Economics, the University of Chicago.

1. Brenner, S.; Brookes, M. C. H., and Roberts, L. J.: The Relation of Liver Stores to the Occurrence of Early Signs of Vitamin A Deficiency in the White Rat, J. Nutrition **23**: 459-471 (May) 1942.

2. The skimmed milk was supplied by the Borden-Wieland Co., Chicago.

3. The halibut liver oil capsules were furnished by Abbott Laboratories, North Chicago, Ill.

4. The regenometer was sent by Dr. Blanchard of the Golden State Co., Ltd., San Francisco.

in that the time required to see a light of fixed intensity is recorded rather than the specific intensities recognized at different time intervals during the dark adaptation period. At weekly and occasionally at biweekly intervals the vitamin A and carotene content of the fasting blood (taken by venipuncture) was determined according to the method of May,[5] 2 cc. of serum being used rather than 1 cc. The blood values were expressed in L_{440} units of carotene and L_{328} units of vitamin A per hundred cubic centimeters of serum corrected for the blue color due to carotene. These values were converted into micrograms of carotene and U. S. P. units of vitamin A respectively by use of the factors determined by Yarbrough and Dann.[6] Blood for total white blood cell counts and differential counts was taken from the ear each week. The counts were made on 200 cells.[7]

The material for microscopic study of the skin[8] was furnished by medium punch biopsy specimens taken from the lateral external portion of the thigh at four and seven month intervals of depletion. Since any thickening of the skin which might occur would decrease the visibility of the capillaries, they were examined with a capillary microscope applied to the cuticle area of the finger two or three times during the experimental period. During the last week of the experiment the eyes of each subject were examined with a slit lamp[9] and the findings recorded according to the system used by Kruse.[10] On the day preceding the termination of the experiment each subject was allowed a measured volume of 95 per cent alcohol (minimum 50 cc.), which was taken with carbonated waters. The effect of the alcohol on the level of vitamin A in the blood was studied four and twelve hours respectively after the intake.

RESULTS

1. Dark Adaptation.—(*a*) Biophotometer: A comparison of the 20 to 30 second dial readings following bleaching of the 6 subjects with similar readings reported by Jeans[11] places 5 of the subjects in the borderline zone (19 to 24) and one in the subnormal zone (below 18). The deficiency diet had little effect on these readings. Although there were slight fluctuations in both directions, i. e. from borderline to normal and subnormal, the subjects maintained their relative groupings (fig. 1).

(*b*) Adaptometer: The cone and rod thresholds for all subjects fell within the normal range reported by Hecht[12] (cone threshold 5.3 to 6.0 log units; rod threshold 2.7 to 3.0 log units). Throughout the entire period these thresholds remained constant for each subject, fluctuating only within the daily variation of 0.3 to 0.4 of a log unit for rod and cone thresholds respectively. In figure 2 are presented the cone and rod thresholds for every test on subject F. W. The data for the other subjects show similar figures.

(*c*) Regenometer: The time necessary to see the five consecutive flashes of the first and second dot for the subjects was well within the normal time limit given by Blanchard,[13] namely, one and three minutes respectively.

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5. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H.: Clinical Studies of Vitamin A in Infants and Children, Am. J. Dis. Child. **59**:1167-1184 (June) 1940.

6. Yarbrough, M. E., and Dann, W. J.: Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey, J. Nutrition **22**:597-607 (Dec.) 1941.

7. Helen Parkes Hunt took all the blood samples and did the blood counts.

8. Dr. S. W. Becker examined the biopsy specimens which were taken in the Dermatology Clinic.

9. Dr. A. C. Krause of the Ophthalmology Department examined the eyes.

10. Kruse, H. D.: The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, Pub. Health Rep. **56**:1301-1324 (June 27) 1941.

11. Jeans, P. C.; Blanchard, M. S., and Zentmire, Z.: Dark Adaptation and Vitamin A, J. A. M. A. **108**:451-458 (Feb. 6) 1937.

12. Hecht, S., and Mandelbaum, J.: Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910-1916 (May 13) 1939.

13. Blanchard, E. L., and Harper, H. A.: Measurement of Vitamin A Status of Young Adults by Dark Adaptation Technic, Arch. Int. Med. **66**:661-669 (Sept.) 1940.

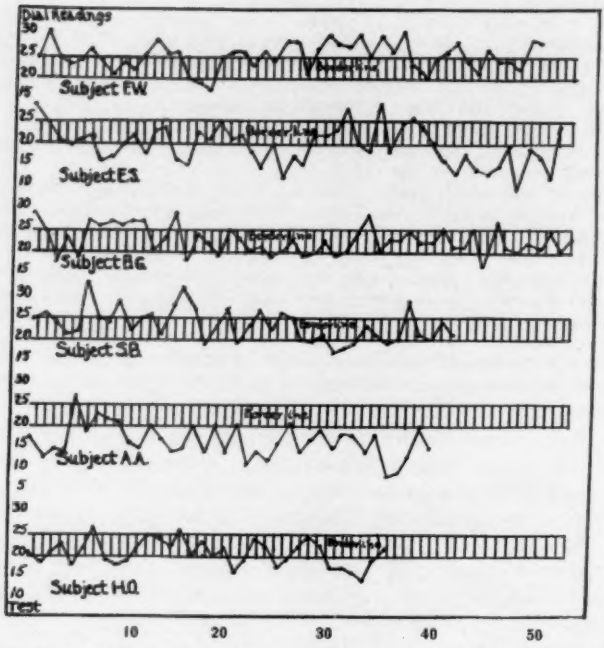

Fig. 1.—Individual biophotometer readings for first test after bleaching during deficiency period.

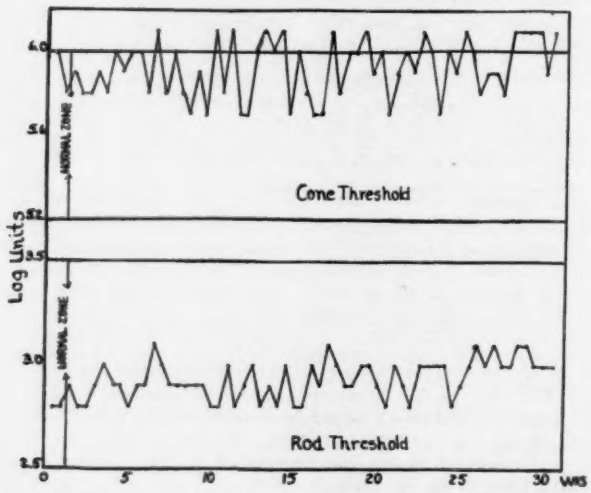

Fig 2.—Cone and rod threshold for each test for subject F. W. Log units refer to intensities in micromicrolamberts.

(*d*) Visual field: The visual field did not seem to be impaired in any way as measured by perimetry.

2. Blood Carotene and Vitamin A.—The vitamin A and carotene content of the blood of all 6 subjects (table 1) prior to the experimental diet compared favorably with that reported by others using the same method.[14] The carotene content of the blood at the outset (139 to 210 micrograms) varied with the dietary habits of the subjects. This did not hold for vitamin A (87 to 150 U. S. P. units). With the deficiency diet the blood carotene showed a steep and immediate drop in the first weeks, and then the rate of loss began to decrease until a plateau was reached. Even at the end of the experiment the blood was not completely free of carotene (30 to 44 micrograms), but this is not to be expected since the vitamin A–low diet did contain small amounts of it. The vitamin A content of the blood, on the other hand, with the exception of small fluctuations, remained at the original level for the duration of the depletion period. Subject S. B., who had the lowest level, continued to have a low level, of approximately 87 U. S. P. units, in spite of the daily consumption of 10,000 units of the vitamin, while the other subjects on their decreased intake maintained higher levels (107 to 150 U. S. P. units)

TABLE 1.—*Carotene and Vitamin A Content per Hundred Cubic Centimeters of Serum Before and After Depletion*

Subject	Sex	Weight, Pounds	Before Depletion		After Depletion	
			Carotene, Micrograms	Vitamin A, U. S. P. Units	Carotene, Micrograms	Vitamin A, U. S. P. Units
S. B.	Female	115	203	87	38	80
B. G.	Female	141	218	112	37	123
E. S.	Female	140	178	107	41	115
F. W.	Female	110	202	126	42	112
A. A.	Male	201	139	150	30	132
H. O.	Male	153	310	119	44	129

than that of the control subject. At times several of the experimental subjects showed unusual rises in the vitamin A content of the blood.

The level of vitamin A in the blood was extremely sensitive to colds and increased body temperature.[15] During the fourth week of the experiment all the subjects, including the control, caught colds and had slight elevations in temperature. The level of the vitamin in the blood reflected this condition by dropping to about one half of the initial value. When the fever disappeared the vitamin A content of the blood resumed its normal level (fig. 3).

Effect of Alcohol on Vitamin A Level of Blood: Table 2 and figure 3 contain a summary of the effects of alcohol on the level of vitamin A in the blood of the women after thirty-one weeks and of the men after twenty weeks of deficiency. Although 50 cc. of alcohol was not a sufficient amount to cause any apparent rises in the vitamin A content of the blood of the experimental subjects, 75 to 100 cc. caused a noticeable rise four hours after consumption. After twelve hours the vitamin A

14. (*a*) Kimble, S. M.: The Photelectric Determination of Vitamin A and Carotene in Human Plasma, J. Lab. & Clin. Med. **24**:1055-1065 (July) 1939. (*b*) May.[5] (*c*) Murrill, W. A.; Horton, P. B.; Lieberman, E., and Newburgh, L. H.: Vitamin A and Carotene Metabolism in Diabetic and Normals, J. Clin. Investigation **20**:395-400 (July) 1941. (*d*) Yarbrough and Dann.[6]

15. Clausen, S. W., and McCoord, A. B.: The Carotenoids and Vitamin A of the Blood, J. Pediat. **13**:635-650 (Nov.) 1938. Thiele, W., and Scherff, I.: Blood Vitamin A Picture in Fever, Klin. Wchnschr. **18**:1275-1277 (Sept. 23) 1939.

in the blood returned to its prealcoholic level in most instances. This would indicate that vitamin A was present in the bodies of the subjects after the depletion period and was capable of being mobilized by the alcohol, as was first demonstrated by Clausen and McCoord.[16]

3. Blood Picture.—According to the reports of Abbott and associates [17] the blood picture should be a valuable aid in the diagnosis of vitamin A deficiency because of the marked changes they obtained in rats and human beings on a vitamin A–low diet, namely, a decreased number of total white blood cells and polymorphonuclears or heterophils and an increased number of lymphocytes with the large lymphocytes predominating over the small. In addition, these authors found many juvenile and stab forms and degenerate cells.

None of the subjects in this study showed this type of picture (table 3). Several times some of the subjects did have a marked lymphocytosis (especially subject

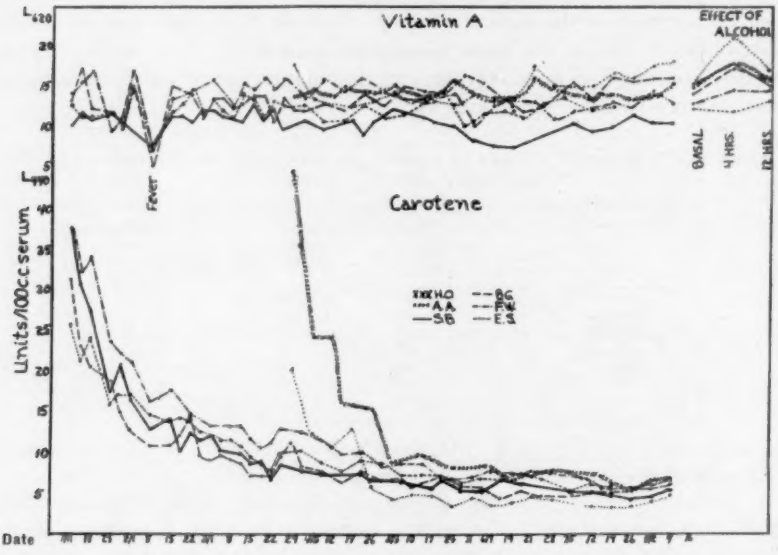

Fig. 3.—Vitamin A and carotene content of individual blood samples. L_{420} units are corrected for blue color due to carotenoids. Subject S. B. was not the control for the alcohol study

A. A.), but always the small lymphocytes predominated over the large and were in the main responsible for this condition. The polymorphonuclears were decreased at these times. Increased total white blood cell counts were not an accompaniment in every case, and at no time were there excess juvenile or degenerate cells. No infectious states were present to account for the increased number of lymphocytes. Further work is necessary to ascertain the significance of the change in

16. Clausen, S. W.; Breese, B. B.; Baum, W. S.; McCoord, A. B., and Rydeen, J. O.: Mobilization of Vitamin A from Its Stores in Tissues by Ethyl Alcohol, Science **91**:318-319 (March 29) 1940; Effect of Alcohol on the Vitamin A Content of Blood in Human Subjects, ibid. **93**:21-22 (Jan. 3) 1941.

17. Abbott, O. D., and Ahmann, C. F.: Effect of Avitaminosis A on the Blood Picture of Albino Rats, Am. J. Physiol. **122**:587-595 (June) 1938. Abbott, O. D.; Ahmann, C. F., and Overstreet, M. R.: Effect of Avitaminosis A on the Human Blood Picture, ibid. **126**: 254-260 (June) 1939.

blood picture in relation to vitamin A, especially since these findings have not been confirmed in their entirety by others.[18]

4. Skin.—The biopsies made at four and seven month intervals of deficiency revealed no measurable differences in the subcutaneous structure of the hair follicles and sweat and sebaceous glands from that found prior to the experimental diet. The visibility of the capillaries remained as good as at the start, demonstrating that there was no keratinization of the epithelial tissue at the regions studied. The detailed findings of this portion of the study will be reported in another paper.

TABLE 2.—*Effect of Alcohol on the Basal Level of Vitamin A in the Blood*

Subject	Alcohol, Cc.	Vitamin A, U. S. P. Units per 100 Cc. Serum After Consumption of Alcohol		
		Basal	4 Hours	12 Hours
Control	50	139	157	136
	75*	142	151	163
E. S.	50	110	107	118
F. W.	50	112	125	127
B. G.	100	123	149	125
A. A.	100	132	181	149
H. O.	150*	129	155	125

* The patient vomited one to one and a half hours after alcohol was taken.

TABLE 3.—*Average Total White Blood Cell and Differential Counts for Ten Week Periods of Depletion*

Subject	Depletion Time, Ten Week Intervals	Total White Cells	Polymorphonuclears	Small Lymphocytes	Large Lymphocytes	Monocytes	Eosinophils	Basophils
S. B.	1st	6,083	111	64	4	15	3	1
	2d	5,978	115	69	5	15	3	1
	3d	5,670	117	53	8	19	2	1
B. G.	1st	10,260	102	78	4	11	5	0
	2d	10,390	96	85	4	9	7	0
	3d	10,310	105	71	8	10	7	1
E. S.	1st	9,360	110	71	5	12	2	0
	2d	7,760	108	75	4	9	3	0
	3d	7,217	105	74	7	11	4	1
F. W.	1st	8,620	112	70	4	12	2	0
	2d	8,430	106	78	4	9	2	0
	3d	8,300	114	65	8	9	2	1
A. A.	1st	9,100	98	86	5	9	2	1
	2d	8,022	97	87	6	8	2	1
H. O.	1st	8,800	121	63	3	11	2	1
	2d	7,745	108	79	5	11	2	1

5. Examination of Eyes.—At the last week of deficiency there were no gross ocular signs. Mild photophobia was present in subjects E. S. and F. W. Examination by slit lamp revealed a subconjunctival tissue slightly less translucent than normal in subjects E. S. and H. O. and a slight engorgement of the posterior conjunctival vessels in subjects B. G. and F. W. The significance of these findings remains obscure, for similar examinations were not made prior to the experimental period. Since Bitot spots, conjunctival foam and changes in vascularity and translucency of the conjunctiva and cornea may occur in persons without vitamin A

18. Wagner, K.: Early Symptoms of Vitamin A Deficiency in Man, Klin. Wchnschr. **19**:567-568 (June 9) 1940.

deficiency as well as in those in all stages preceding severe vitamin A deficiency, these signs are suggestive but not positive indications of deficiency.

6. Subjective Signs.—The general health of the subjects throughout the experiment was as usual. There were one or two colds during the winter, but this was no more than in previous years. There were no reports by the subjects of subjective night blindness. One (subject B. G.) complained of excessive fatigue which was most likely due to her heavy schedule and late hours.

COMMENT

It is seen, therefore, that normal, well fed adults did not present any of the alleged signs of subclinical vitamin A deficiency even after seven and one-half months on a depletion diet. Either or both of two factors may be responsible for such a result. Either the demand for vitamin A by the organism is not great enough to cause sufficient depletion of normal hepatic stores in seven and one-half months to result in the occurrence of the reported early signs of vitamin A deficiency, or these signs are not solely a result of uncomplicated vitamin A deficiency.

That an extensive degree of depletion of stores of vitamin A is a prerequisite for the development of the subclinical signs of deficiency is borne out by animal studies in which the occurrence of these signs has been correlated with liver stores, by the greater prevalence of subclinical signs in children than in adults and in males than in females and by the relatively low incidence of defects in populations on vitamin A–meager diets. In rats it has been shown that a lag exists between the exhaustion of hepatic stores and the appearance of loss of weight and xerophthalmia.[19] In children and males the amount of vitamin A storage is less than in adults and females—in children because they have had less opportunity to acquire stores; in males (if a sex difference is accepted) because they store less and lose it more readily than females, as was shown in rats.[20] Steven's and Wald's investigation in Labrador [21] revealed only a small percentage of night blindness, although to judge from the habitual dietaries a much greater percentage would have been expected. Josephs' [22] study of the vitamin A content of the blood and dark adaptation in various socioeconomic groups showed that only in severe and prolonged vitamin A deficiency were these measurements affected. The failure for as long as six months of controlled vitamin A–low diets to result in any of the specific signs of deficiency [23] is also indicative that the depletion period studied

19. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **32**:11-32 (July) 1941. Horton, P. B.; Murrill, W. A., and Curtis, A. C.: The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, J. Clin. Investigation **20**:387-393 (July) 1941. Brenner, Brookes and Roberts.[1]

20. Bult, A. R., and Sorgdrager, C. J.: Influence of Sex and Castration in Male Rats upon Vitamin A Metabolism, Chem. Abstr. **38**:775 (Feb. 10) 1941. Brenner, Brookes and Roberts.[1]

21. Steven, D., and Wald, G.: Vitamin A Deficiency: Field Study in Newfoundland and Labrador, J. Nutrition **21**:461-476 (May) 1941.

22. Josephs, H. W.; Baber, M., and Conn, H.: Studies in Vitamin A: The Relation of Blood Level and Adaptation to Dim Light to Diet, Bull. Johns Hopkins Hosp. **68**:375-387 (May) 1941.

23. (*a*) Steininger, G., and Roberts, L. J.: Biophotometer Test as Index of Nutritional Status for Vitamin A, Arch. Int. Med. **64**:1170-1186 (Dec.) 1939. (*b*) Isaacs, B. C.; Jung, F. T., and Ivy, A. C.: Clinical Studies of Vitamin A Deficiency, Arch. Ophth. **24**:

was not ample. It is interesting to note that a theoretic calculation based on the average vitamin A content of human liver [24] and the assumption that the rate of use is approximately 2,000 U. S. P. units per day shows that it would take from one to two years for the liver to lose its entire vitamin A stores if no vitamin A were present in the diet.

The second explanation offered for the negative findings of this study is that these signs are neither sensitive nor specific for subclinical vitamin A deficiency. The contradictory evidence concerning their diagnostic value supports such a contention.

In respect to dark adaptation it has been shown that there is an inconsistency in the response of normal subjects to vitamin A–low diets in the various laboratories as well as in the response of deficient subjects to massive doses of vitamin A.[25] The specificity of night blindness as an indication of vitamin A deficiency has also been challenged by the curative effect of vitamin C and riboflavin in some cases.[26] There are indications, too, that several of the other symptoms may be more sensitive than dark adaptation as indicators of subclinical vitamin A deficiency.[27] This is quite conceivable, since animal experimentation reveals that the vitamin A content of the retina persists even in the absence of hepatic stores.[28]

Two additional alleged subclinical signs which have received a reasonable share of attention are the decreased vitamin A content of the blood and changes in the structure of the skin. The former has obtained support from the work of May,[5] Lewis, Bodansky and Haig [27c] and Yarbrough and Dann.[6] These investigators found the blood level the most sensitive indicator of vitamin A deficiency. On the other hand, Josephs [22] and Nylund [23d] with human beings and Brenner, Brookes and Roberts [1] with rats found that there is a wide range in the blood level of normal subjects and that only in prolonged and severe deficiency is the blood level valuable diagnostically. Changes in the skin, such as keratinization and resulting horny papules known as toadskin, have been reported by Lehman [29] in

698-721 (Sept.) 1940. (*c*) Steffens, L. F.; Bair, H. L., and Sheard, C.: Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, Proc. Staff Meet., Mayo Clin. **14**:698-704 (Nov.) 1940. (*d*) Nylund, C. E., and With, T. K.: Demonstration of Vitamin A Deficiency in Man, Acta med. Scandinav. **106**:202-228, 1941. (*e*) Murrill, Horton, Lieberman and Newburgh.[14c]

24. Abels, J. C.; Gorham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Gastrointestinal Cancer: III. The Hepatic Concentration of Vitamin A, Proc. Soc. Exper. Biol. & Med. **48**:488-492 (Nov.) 1941.

25. (*a*) Booher, L. E.; Callison, E. E., and Hewston, E. M.: An Experimental Determination of the Minimum Vitamin A Requirement of Normal Adults, J. Nutrition **17**:317-331 (April) 1939. (*b*) Wald, G., and Stevens, P.: An Experiment in Human Vitamin A Deficiency, Proc. Nat. Acad. Sc. **25**:344-349 (Aug.) 1939. (*c*) Steininger, and Roberts.[23a] (*d*) Isaacs, Jung and Ivy.[23b] (*e*) Hecht, S., and Mandelbaum, J.: Dark Adaptation and Experimental Human Vitamin A Deficiency, Am. J. Physiol. **130**:651-664 (Oct.) 1940. (*f*) Steffens, Bair and Sheard.[23c] (*g*) Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, J. Pediat. **18**: 170-194 (Feb.) 1941.

26. Stewart, C. P.: Nutritional Factors in Dark Adaptation, Edinburgh M. J. **48**:217-237 (April) 1941.

27. (*a*) May, Blackfan, McCreary and Allen.[5] (*b*) Steffens, Bair and Sheard.[23c] (*c*) Lewis, J. M.; Bodansky, O., and Haig, C.: Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and Children, Am. J. Dis. Child. **62**:1129-1148 (Dec.) 1941. (*d*) Yarbrough and Dann.[6]

28. Greenberg, R., and Popper, H.: Demonstration of Vitamin A in the Retina by Fluorescence Microscopy, Am. J. Physiol. **134**:114-118 (Aug.) 1941. Brenner, Brookes and Roberts.[1]

29. Lehman, E., and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children, J. A. M. A. **114**:386-393 (Feb. 3) 1940.

children on relief and by Steffens, Bair and Sheard [23c] in an adult maintained on a vitamin A–low diet for one hundred and eighty days. This condition has been described as occurring in scurvy, pellagra and other deficiency diseases,[30] the more severely affected patients being from the Orient, where the diet is totally inadequate in all the dietary constituents.[31] Since the deficiencies are multiple, the assumption that the lack of vitamin A alone is responsible for the cutaneous changes is not justified, even though massive doses of vitamin A have been effective in causing a cure, for in general other concentrates are also administered.

Moore [30c] in summing up the allowable claims for vitamin A deficiency stated:

> If, therefore, the claim that phrynoderma (toadskin) is acceptable as a manifestation of vitamin A deficiency, it is difficult to understand how night blindness can be accepted as an early or invariable symptom of vitamin A deficiency. But is phrynoderma due to a deficiency of vitamin A? There are a number of observers who hold it is not so.

From these existing uncertainties it is evident that much work needs yet to be done on the metabolism of vitamin A to elucidate the confusing evidence.

SUMMARY

Five young adults, 3 women and 2 men, were placed on a vitamin A–low diet for seven and one-half and four and one-half months respectively. At suitable intervals measurements were made of dark adaptation, blood vitamin A and carotene, total white blood cell counts and differential blood counts and changes in the structure of skin and conjunctivas. None of these measurements showed any definite changes from those found prior to the deficiency for the length of time studied. It appears, then, either that these subjects had sufficient stores to withstand the effects of the depletion diet or that these signs are not merely the result of uncomplicated vitamin A deficiency.

Drs. Becker, Krause and Oldham and Mrs. Helen Parkes Hunt gave cooperation in the work on this problem.

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30. (*a*) Scheer, M., and Keil, H.: Follicular Lesions in Vitamin A and C Deficiency, Arch. Dermat. & Syph. **30**:177-185 (Aug.) 1934. (*b*) Keil, H.: The Follicular Lesions of Vitamin A and C Deficiency: A Critical Survey, Am. J. Digest. Dis. **5**:40-48 (March) 1938. (*c*) Moore, F. D.: Allowable Claims for Vitamin A Deficiency: The Relation of Visual Defect and Skin Lesions, J. Trop. Med. & Hyg. **44**:47-48 (April 15) 1941.

31. Frazier, C. N., and Hu, C. K.: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency, Arch. Dermat. & Syph. **33**:825-852 (May) 1938.

EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

IV. ISOLATION AND IDENTIFICATION OF URINARY COPROPORPHYRIN ISOMERS

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Protoporphyrin III constitutes the prosthetic group of certain vital substances, notably hemoglobin.[1] Only porphyrins of isomeric series I and III occur naturally in plants and animals, and Fischer [2] pointed out that it is inconceivable for porphyrins of types I and III to be transformed one to the other in any biologic process, that they must be formed individually in the physiologic synthesis. Porphyrin arises in the body during synthesis of hemoglobin rather than during its destruction, as had been supposed formerly, a small proportion of isomeric series I arising as a by-product of the main synthesis of isomeric series III intended for utilization in the manufacture of hemoglobin.[3] The porphyrin of isomeric series I is not utilized and is excreted as coproporphyrin I, and any porphyrin of isomeric series III which has been synthesized in greater amounts than are necessary to meet the immediate requirements, or which is prevented from entering into the synthesis of hemoglobin by a toxic block, such as occurs with lead poisoning, is excreted as coproporphyrin III. Thus both coproporphyrins I and III might occur in the normal urine as well as pathologically. It was supposed formerly [4] that only coproporphyrin I was excreted normally in the urine, until

Abstract of portion of thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Medicine.

1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, ed. 2, Baltimore, Williams & Wilkins Company, 1939. Carrié, C.: Die Porphyrine: Ihr Nachweis, ihre Physiologie und Klinik, Leipzig, Georg Thieme, 1936. Mason, V. R.; Courville, C. B., and Ziskind, E.: The Porphyrins in Human Disease, Medicine **12**:355-439 (Dec.) 1933. Morhardt, P. E.: Les porphyrines et leur rôle physio-pathologique, Presse méd. **2**:1200-1202 (Aug. 12) 1931. Vannotti, A.: Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

2. Fischer, H.: Hämin, Bilirubin und Porphyrine, Naturwissenschaften **18**:1026-1037 (Nov. 28) 1930; Ueber Blut, Blatt und Gallenfarbstoff, in Oppenheimer, C.: Handbuch der Biochemie des Menschen und der Tiere, ed. 2, Jena, Gustav Fischer, 1930, supp., p. 72; Ueber Hämin und Porphyrine. Verhandl. d. deutsch. Gesellsch. f. inn. Med. **45**:7-27, 1933.

3. (*a*) Dobriner, K.: Porphyrin Excretion in Feces in Normal and Pathological Conditions, J. Biol. Chem. **120**:115-127 (Aug.) 1937. (*b*) Dobriner, K., and Rhoads, C. P.: The Metabolism of Blood Pigments in Pernicious Anemia, J. Clin. Investigation **17**:95-103 (Jan.) 1938. (*c*) Dobriner, K.; Strain, W. H.; Localio, S. A.; Keutmann, H., and Stephens, D. I.: II. Coproporphyrin I Metabolism and Hematopoietic Activity, Proc. Soc. Exper. Biol. & Med. **36**:755-756 (June) 1937. (*d*) Rimington, C.: Porphyrins and Their Relation to the Metabolism of Blood Pigments, Proc. Roy. Soc. Med. **32**:1268-1275 (Aug.) 1939. (*e*) Lemberg, R.: Transformation of Haemins into Bile Pigments, Biochem. J. **29**:1322-1336 (June) 1935.

4. (*a*) Fink, H., and Hoerburger, W.: Isolierung von kristallisiertem Koproporphyrin I aus normalem menschlichem Urin, Naturwissenschaften **22**:292 (April 27) 1934. (*b*) Watson, C. J.: Concerning the Naturally Occurring Porphyrins: IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with that Excreted Normally and in Other Diseases, J. Clin. Investigation **15**:327-334 (May) 1936.

Grotepass [5] isolated both coproporphyrin I and III from the urine of healthy persons. Since a possibility still exists that hemoglobin in the diet may afford an exogenous source of coproporphyrin III in the urine, Watson [6] suggested that a study similar to that of Grotepass, but carried out on the urine of subjects on a meat-free diet, would be of extreme importance.

The coproporphyrin is excreted by the liver and kidneys, the ratio of urinary excretion to fecal excretion depending chiefly on the patency of the bile passage and the efficiency of the liver, which is the more important organ of excretion. Normally only a small fraction of the total coproporphyrin excreted appears in the urine,[7] but this fraction is increased in the event of biliary obstruction or parenchymatous hepatic damage, a mechanism similar, indeed, to the excretion of bile pigments.

Reports have varied in those instances of hepatic disease in which the urinary coproporphyrin has been isolated and the isomeric type identified. The question arises whether the findings have been representative of hepatic damage or biliary obstruction in general, or whether they are related to some complicating circumstance in the particular cases investigated. Coproporphyrin I has been isolated from the urine of 20 patients suffering from such diseases as cinchophen cirrhosis, atrophic cirrhosis, hemolytic icterus, biliary obstruction, chronic passive congestion, lymphosarcoma of the liver, Hodgkin's disease involving the bile passage and catarrhal or infectious jaundice.[8] Coproporphyrin III has been isolated in 4 instances, including 1 case each of melanosarcoma of the liver and hemochromatosis and 2 cases of atrophic cirrhosis.[9] The patient in one of the 2 latter cases had been receiving mercury for the treatment of syphilis, and because of this complicating toxic factor perhaps this case should not be included.

The present investigation represents the study of 10 patients who had various diseases of the liver or bile ducts, including carcinoma of the common bile duct, carcinoma of the head of the pancreas with biliary obstruction, obstructive biliary cirrhosis due to stone in the common duct, syphilitic hepatitis plus biliary cirrhosis due to stone in the common duct, hepatic metastasis from carcinoma of the rectum, subacute atrophy of the liver, atrophic cirrhosis and alcoholic cirrhosis. All these

5. Grotepass, W.: Zur Kenntnis der natürlichen Harnporphyrine, Ztschr. f. physiol. Chem. **253**:276-280, 1938.

6. Watson, C. J.: Porphyrins and Diseases of Blood, in a Symposium on Blood and Blood-Forming Organs, Madison, University of Wisconsin Press, 1939, pp. 14-30.

7. Dobriner, K., and Rhoads, C. P.: The Quantitative Determination of Urinary Coproporphyrin, New England J. Med. **219**:1027-1029 (Dec. 29) 1938. Watson, C. J.: Concerning the Naturally Occurring Porphyrins: I. The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, J. Clin. Investigation **14**:106-109 (Jan.) 1935. Nesbitt, S., and Snell, A. M.: The Excretion of Coproporphyrin in Hepatic Disease: I. Urinary and Fecal Excretion as Correlated with Parenchymatous Hepatic Damage, Arch. Int. Med. **69**:573-581 (April) 1942; The Excretion of Coprophorphyrin in Hepatic Disease: II. Urinary and Fecal Excretion in Biliary Obstruction, ibid. **69**:582-588 (April) 1942. Dobriner.[3a] Watson.[4b]

8. (*a*) Dobriner, K.: Urinary Porphyrin in Disease, J. Biol. Chem. **113**:1-10 (Feb.) 1936. (*b*) Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, Physiol. Rev. **20**:416-468 (July) 1940. (*c*) Tropp, C., and Penew, L.: Quantitative klinische Harnporphyrinuntersuchungen: II. Mitteilung. Lebercirrhosen, Hepatopathien (ausser Cirrhosen), Tuberkulose und andere Krankheiten, Deutsches Arch. f. klin. Med. **180**:411-422, 1937. (*d*) Vigliani, E. C., and Libowitzky, H.: Ueber Porphyrine im Harn und im Kot, Klin. Wchnschr. **16**:1243-1245 (Sept. 4) 1937. (*e*) Watson, C. J.: Concerning the Naturally Occurring Porphyrins: II. The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces of a Case of Familial Hemolytic Jaundice, J. Clin. Investigation **14**:110-115 (Jan.) 1935.

9. Dobriner.[8a] Vigliani and Libowitzky.[8d]

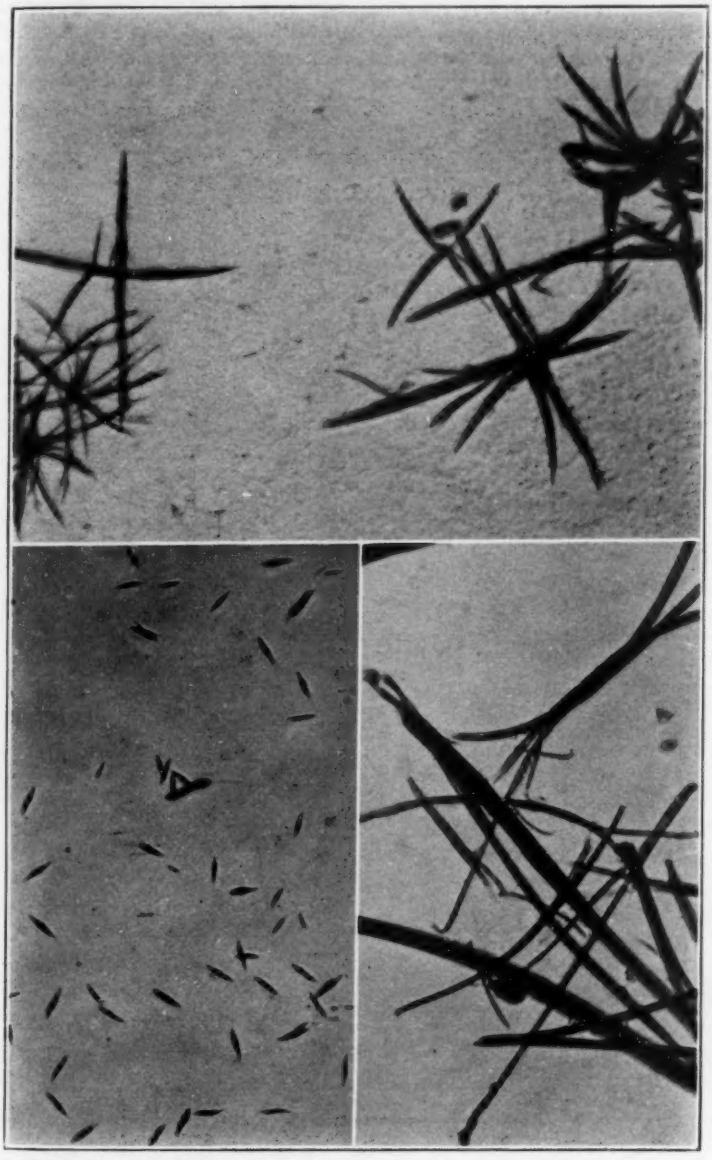

Fig. 1.—Crystals of coproporphyrin I methyl ester (× 800).

patients were on a completely meat-free diet throughout the period of observation. The urinary coproporphyrin was isolated and esterified by the method described by Grotepass,[5] and the melting point of the methyl ester was determined with the Johns micro melting point apparatus manufactured by the Fisher Scientific Company. This method of isolation of coproporphyrin could not be considered at

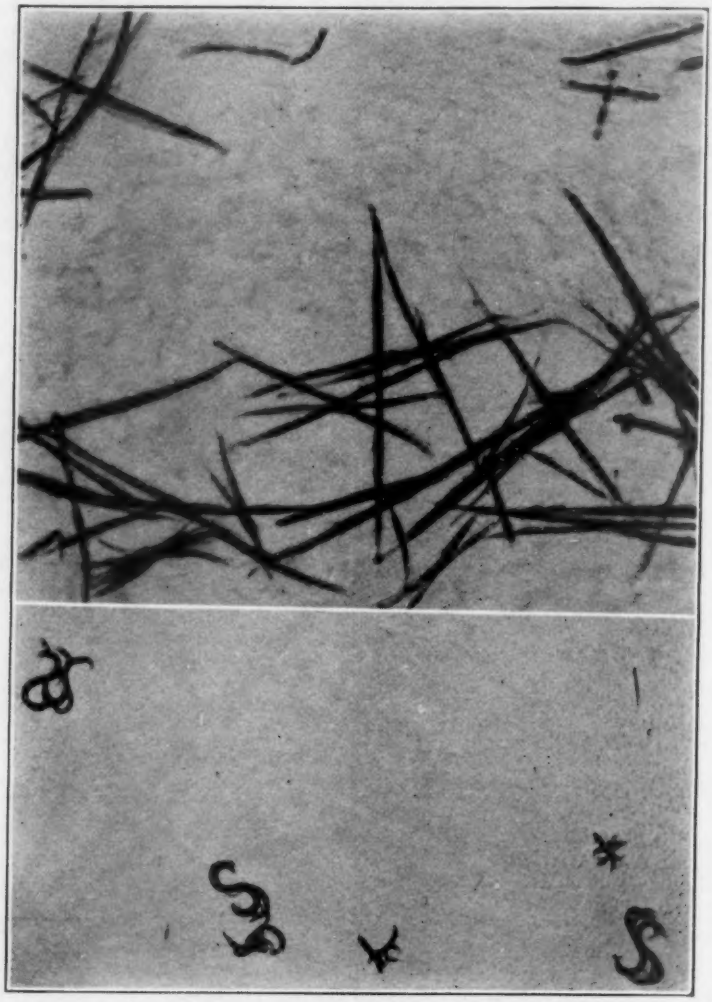

Fig. 2.—Crystals of coproporphyrin III methyl ester (× 800).

all a quantitative procedure, but was used only as a means of determining the isomeric type. It was obvious that considerable loss occurred during the time of collection and adsorption, as well as during the process of purification and isolation. Figure 1 represents several photomicrographs of crystals of coproporphyrin I which were isolated during this study, and figure 2 represents photo-

micrographs of crystals of coproporphyrin III. Study of the crystalline structure is interesting but is too unreliable to be of any great assistance. Table 1 represents the melting points of the coproporphyrin isomers I and III, as reported by various investigators.

The results of the present investigation are shown in table 2. In cases 1 and 2 the patients had obstructive jaundice, and coproporphyrins I and III were obtained

TABLE 1.—*Melting Points of the Methyl Esters of Coproporphyrins I and III in Degrees Centigrade*

References	Coproporphyrin I	Coproporphyrin III *	
Dobriner [3a]	252	142	172
Chandler, F. G.; Harrison, G. A., and Rimington, C.: Brit. M. J. **2**: 1173, 1939	252	145	172
Fischer, H., and Neumann, F. W., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 527-534. Fischer H., and Hierneis, J.: Ztschr. f. physiol. Chem. **196**: 155, 1931	250	145	165
Rimington, C.: Lancet **1**: 770, 1938; Onderstepoort J. Vet. Sc. **7**: 567, 1936	245	144-146	169-172

* Coproporphyrin III possesses a double melting point in that it may first melt at the lower temperature and after cooling melt at the higher temperature.

TABLE 2.—*Presentation of Cases and Certain Data*

Case	Diagnosis	Range of Urinary Coproporphyrin, Micrograms	Days Observed	Coproporphyrin Fraction as Isolated	Weight, Mg.	Melting Point, Degrees C.
1	Carcinoma of common bile duct with complete obstruction	79-615	16	1 Coproporphyrin I	1.3	248
				2 Coproporphyrin I	1.0	240
				3 Coproporphyrin III	*	166
2	Carcinoma of head of pancreas with complete common duct obstruction	20-282	19	1 Coproporphyrin I	0.7	240
				2 Coproporphyrin III	0.3	138
				3 Coproporphyrin III	*	165
3	Obstructive biliary cirrhosis, common duct stone	50-178	21	1 Coproporphyrin I	0.1	245
				2 Coproporphyrin I	*	215
4	Hepatitis (syphilis), biliary cirrhosis (common duct stone)	76-280	9	1 Coproporphyrin I	0.1	243
				2 Coproporphyrin III	*	165
5	Hepatic metastasis from carcinoma of rectum	190-520	8	1 Coproporphyrin I	0.2	247
				2 Coproporphyrin I	*	243
6	Subacute atrophy of liver	115-600	49	1 Coproporphyrin I	1.8	247
				2 Coproporphyrin III	1.25	165
				3 Coproporphyrin III	*	170
7	Atrophic cirrhosis of liver (unknown cause)	100-630	17	1 Coproporphyrin I	0.2	243
				2 Coproporphyrin I	*	236
				3 Coproporphyrin I	*	254
8	Alcoholic cirrhosis	400-782	5	1 Coproporphyrin III	1.1	140
				2 Coproporphyrin III	*	138
9	Alcoholic cirrhosis	100-600	93	1 Coproporphyrin I	4.0	243
				2 Coproporphyrin I	1.2	240
				3 Coproporphyrin III	1.0	167
10	Alcoholic cirrhosis	414-838	48	1 Coproporphyrin I	1.6	242
				2 Coproporphyrin III	1.1	170

* Too small an amount to weigh.

from the urine. In case 3 the patient had obstructive jaundice with considerable biliary cirrhosis and coproporphyrin I only was obtained. Coproporphyrins I and III were isolated from the urine of a patient who had syphilitic hepatitis complicated by a certain amount of biliary cirrhosis (case 4). Coproporphyrin I only was obtained from the urine of a patient who had extensive hepatic metastasis from carcinoma of the rectum (case 5). From the urine of a patient who had subacute atrophy of the liver coproporphyrins I and III were isolated (case 6), and copro-

porphyrin I alone was isolated from the urine of a patient who had atrophic cirrhosis of the liver of unknown cause (case 7). The urine from 3 patients who had alcoholic cirrhosis of the liver was examined; in 2 instances both coproporphyrin I and coproporphyrin III were isolated, but in 1 instance coproporphyrin III alone was demonstrated.

SUMMARY AND CONCLUSIONS

Ten patients who had various types of hepatic damage or biliary obstruction and who were maintained on a meat-free diet were studied. The urinary coproporphyrin of these patients was isolated and the isomeric type determined. From the urine of 6 of these patients, more than half of those on whom such studies were undertaken, both coproporphyrin I and coproporphyrin III were isolated. In 3 instances (cases 1, 4 and 9) coproporphyrin III represented but a relatively small fraction of the total coproporphyrin which was isolated, whereas in 3 other instances (cases 2, 6 and 10) a greater proportion of the coproporphyrin isolated was coproporphyrin III. In 3 cases (3, 5 and 7) coproporphyrin I alone was isolated, and in but a single case (8) was coproporphyrin III alone isolated. In each instance an appreciable quantity of coproporphyrin remained in the mother liquor, which was deeply colored. In all probability this was the methyl ester of coproporphyrin III, which crystallizes with considerably more difficulty than does the methyl ester of coproporphyrin I. It is possible that by the use of a more quantitative procedure, such as was described recently by Watson,[10] both coproporphyrin I and coproporphyrin III might be demonstrated in the urine of all or most patients who have hepatic disease. The occurrence in the urine of these patients of coproporphyrin I, either alone or with additional varying proportions of coproporphyrin III, is in accord with the current hypotheses of synthesis and excretion of porphyrin. It is difficult on this basis to explain the excretion of coproporphyrin III alone, which occurred in but 1 instance.

The Mayo Clinic.

10. Watson, C. J., and Schwartz, S.: A Method of Separating Small Quantities of the Coproporphyrin Isomers 1 and 3, Proc. Soc. Exper. Biol. & Med. **44**:7-10 (May) 1940.

COPPER AND IRON IN HUMAN BLOOD

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Copper and iron are essential elements in the human organism, and recent enlightening research has given increased evidence of their importance in the blood stream.

In our first experiments, nine years ago, on the iron content of whole blood, we found it necessary to establish a large series of determinations on normal persons.[1] The average iron content of whole blood for 200 men was 50.13 ± 0.15 mg. per hundred cubic centimeters, and for 100 women it was 43.42 ± 0.19. The mathematical index, the mode, the figure which appears most frequently in the series of determinations and around which the majority of figures group themselves, was 50 mg. of iron per hundred cubic centimeters for 200 men and 45 mg. for 100 women.[1b] The fact that in women the average fell below the mode illustrates the tendency toward the anemic state in women.

The determination of iron in whole blood is an accurate method of hemoglobin determination, and it compares favorably with the accepted method of determining oxygen capacity.[2] Iron represents 0.335 per cent by weight of the hemoglobin molecule. This is called the Butterfield factor:[3]

$$\text{hemoglobin} = \frac{\text{mg. of iron in 100 cc. of blood}}{3.35} = \text{Gm. of hemoglobin in 100 cc. of blood.}$$

In our series the normal hemoglobin value based on determinations of iron in the blood of 200 men was 14.96 ± 0.045 Gm. per hundred cubic centimeters of blood. For 100 women the normal value was 12.96 ± 0.06 Gm. We agree with other investigators that in the estimation of hemoglobin it is impossible to assume a normal standard for men, women and children.

Children[4] follow a different standard than adults, especially during the first year of life. They follow a curve rather than a single standard, if the figures are to be expressed on a percentage basis. We found that the curve for the iron content of whole blood followed the pattern of the curves that others reported for

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1. (*a*) Sachs, A.; Levine, V. E., and Appelsis, A.: Iron in Human Blood, Arch. Int. Med. **52**:366 (Sept.) 1933. (*b*) Sachs, A.; Levine, V. E., and Fabian, A. A.: Copper and Iron in Human Blood, ibid. **55**:227 (Feb.) 1935.

2. Karshan, M., and Freeman, R. G., Jr.: Study of Hemoglobin Methods, J. Lab. & Clin. Med. **15**:74 (Oct.) 1929.

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the hemoglobin content.[5] There is a sudden drop in both iron and hemoglobin immediately post partum and a secondary drop in the third month of life. The immediate drop of hemoglobin is supposedly due to a physiologic adaptation of the newborn infant to its extrauterine environment, and the secondary drop may be due to an iron depletion of the storehouses or it may represent the point in an infant's life at which adjustment finally is made in the digestive and absorptive processes to insure the utilization of the extrinsic supply of hemopoietic agents.

HEMOGLOBIN CURVES

After the first year of life, the iron curve shows nothing unusual other than a gradual rise to the level for adults. It is necessary to follow this curve so that proper indications for iron therapy may be thoroughly understood. No amount of iron therapy thus far recorded has seemed to influence this sudden drop in the hemoglobin at birth. The difference in iron and hemoglobin values for sex are not observed until after adolescence.

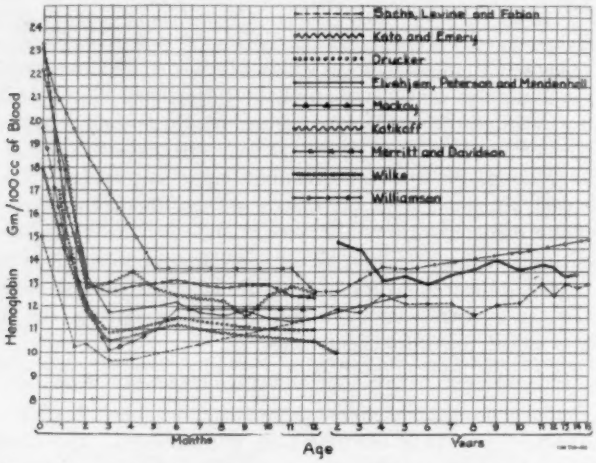

Fig. 1.—Hemoglobin values for blood of normal children, reported by various authors.

If for clinical purposes one wishes to follow a common standard, which represents 100 per cent hemoglobin, for men, women and children, some formula or modification may be of value, because they each present a separate picture. Excluding iron values for newborn infants, the series of 71 specimens from children

5. (*a*) Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916. (*b*) Wilke, E.: Ueber den Gehalt des Blutes gesunder Kinder vom zweiten bis vierzehnten Lebensjahr an roten Blutkörperchen, an Blutfarbstoff, an Retikulocyten und an Thrombocyten, Folia haemat. **52**:291, 1934. (*c*) Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life, Am. J. Dis. Child. **46**:990 (Nov.) 1933. (*d*) Kotikoff, I. A.: Ueber den Eisengehalt im Blute der Säuglinge, Jahrb. f. Kinderh. **132**:180 (July) 1931. (*e*) Mackay, H. M. M.: The Normal Hemoglobin Level During the First Year of Life: Revised Figures, Arch. Dis. Childhood **8**:221 (June) 1933. (*f*) Elvehjem, C. A.; Peterson, W. H., and Mendenhall, D. R.: Hemoglobin Content of the Blood of Infants, Am. J. Dis. Child. **46**:105 (July) 1933. (*g*) Drucker, P.: Investigations on the Normal Values for the Hemoglobin and the Cell Volume in the Small Child, Acta pædiat. **3**:1, 1923. (*h*) Kato, K., and Emery, O. J.: Hemoglobin Content of the Blood in Infancy, Folia haemat. **49**:106, 1933.

averaged 40.61 mg. of iron per hundred cubic centimeters of whole blood. The ages were from 1½ months to 15 years.

Fifty milligrams of iron for normal males, 45 mg. for females and 40 mg. for children of both sexes up to 15 years of age represent the mode for the iron content of whole blood. By means of the Butterfield [3] factor it was determined that 71 children had 12.10 Gm. of hemoglobin per hundred cubic centimeters of blood. A normal child would thus register 80 per cent hemoglobin on the ordinary clinical hemoglobinometer, which employs one standard for comparison of all bloods, regardless of age or sex of the subject. We have used the following formulas:

Milligrams of iron in 100 cc. of blood × 2 = per cent hemoglobin for men
Milligrams of iron in 100 cc. of blood × 2.22 = per cent hemoglobin for women
Milligrams of iron in 100 cc. of blood × 2.50 = per cent hemoglobin for children

Figure 2 shows the curves made from determinations of copper and iron in the blood from birth to adult life and also shows that the content of each in the blood of both males and females remains the same up to the age of puberty. It

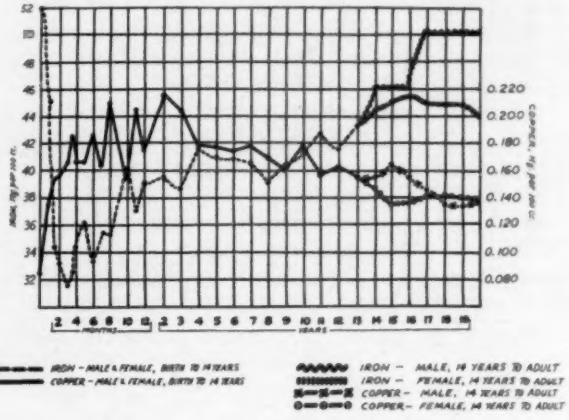

Fig. 2.—Values of copper and iron in the blood of males and females from birth to the adult state.

likewise shows that the iron content reaches the adult level earlier in females than in males. In girls after the fourteenth or fifteenth year of life the values for iron and hemoglobin become rather constant and assume the adult state, while, on the other hand, in boys they increase only slightly between the ages of 14 and 16 but rise sharply after the sixteenth year to reach the real adult state by the seventeenth year. The copper values follow the same scheme in reaching the adult level. This is in accord with other evidences of earlier maturity in girls. The level of iron in the blood of children is 20 per cent lower than that in adults, but the relationship of iron and copper is maintained. The hypoferronemic picture is accompanied by a relative hypercupremic picture, and the hypocupremia of the newborn is associated with hyperferronemia.

The inverse relationship of the copper and the iron content of whole blood is true from infancy throughout adult life and likewise in practically all types of anemia that we have thus far encountered.

The reciprocal relationship of copper and iron is best shown in observations on patients with polycythemia, whose red blood cells and hemoglobin values can be

readily reduced by phenylhydrazine. Hypoferronemia was followed by hypercupremia, and hyperferronemia was followed by hypocupremia. This is best shown in figure 3.

In experimental hemorrhage in dogs and in the massive hemorrhage of peptic ulcer the reciprocal relationship of copper and iron is again emphasized.[6] Elvehjem [7] and the Wisconsin group have called attention to the action of copper and iron in synthesis of hemoglobin, and we feel that the reciprocal relationship of copper and iron also emphasizes the importance of copper. It acts as a catalyzer and likewise must aid in the mobilization of iron when needed from its storehouse. The fetal liver is the most important storage organ for both copper and iron. The fetal liver contains six to ten times as much copper per kilogram of weight as the adult liver. Sheldon [8] stated that 7 mg. of copper is stored in the liver of the newborn infant.

A normal mother constantly supplies the fetal liver with both iron and copper. The blood volume increases during pregnancy and at term rises to the extent

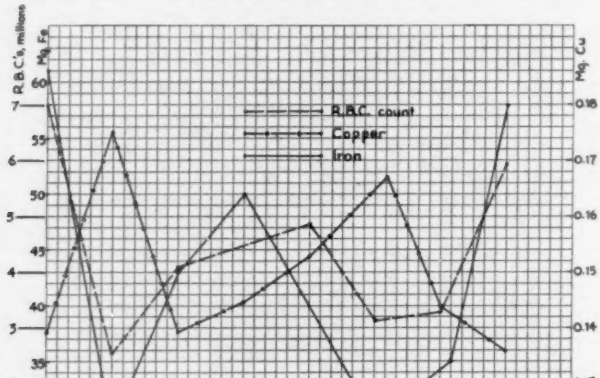

Fig. 3.—Fluctuation of iron and copper values in the blood of a patient with polycythaemia vera.

of 23 per cent. The total amount of copper in the blood stream during pregnancy may be almost twice the amount in the nongravid state.

The iron content of whole blood during pregnancy was of two significant types: one was normal or slightly below normal, and the second showed a true anemia. Both types were accompanied by a high copper level. The average iron content of 25 pregnant women [1b] was 40.44 mg. per hundred cubic centimeters of blood, which is a figure below the normal, 45 mg., for nonpregnant women. This relative anemia, or physiologic anemia, as it is called by some, varies in different women and may be combated by iron therapy.

6. Sachs, A.: The Effect of Bleeding Ulcers and Hemorrhagic Anemia upon Whole Blood Copper and Iron, Am. J. Digest. Dis. & Nutrition **4**:803 (Feb.) 1937.

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8. Sheldon, J. H.: Some Consideration on the Influence of Copper and Manganese on the Therapeutic Activity of Iron, Brit. M. J. **2**:869 (Nov. 12) 1932.

The average copper content of 25 pregnant women was 0.195 mg. per hundred cubic centimeters of blood, which is far greater than the normal, 0.131 mg. per hundred cubic centimeters of whole blood, for nonpregnant women. The hypercupremia of pregnancy when associated with a normal iron content is physiologic and reflects the normal mechanism of transporting copper from the maternal blood to the fetal reservoirs. The hypercupremia of pregnancy when accompanied by a hypoferronemia may represent not only this mechanism but also mobilization of copper to combat the anemia which is commonly found in some pregnant women.

The fetus, on the other hand, has a low copper content of the blood and a relatively high iron content. This high iron content is maintained even when the maternal blood shows definite hypoferronemia. The average iron content of fetal blood was 54.34 mg. per hundred cubic centimeters, while the average copper content was 0.098 mg. These figures may vary slightly but represent a fairly normal average. After diffusion of the copper through the placenta, the fetus does not retain most of this element in the blood stream but evidently stores it in the liver.

The polycythemia of newborn infants was not evident in our series. The blood counts reported by several authors varied because some used cord blood and others used capillary blood for the counts. Erythrocyte counts on capillary blood are universally higher than counts on cord blood. Our averages show that capillary counts exceed cord counts by 1,000,000 cells per cubic millimeter in normally born infants and by 700,000 in infants born by cesarean section.[9]

The reciprocal relationship of copper and iron is present in all forms of anemia that we have been privileged to examine. We have thus far never encountered a deficiency of copper, and it is rather difficult to conceive how a true deficiency could exist, unless a very abnormal nutritional state were present. The small amount of copper required daily and its occurrence in all foods, in water, in beverages, in iron compounds and even in dust make the intake ample. Starvation, high intestinal fistulas and extremely severe diarrhea are possible factors encouraging a deficiency of copper, but as yet no one has definitely shown a deficiency of this element in the blood stream of a human being.

The inverse relationship of copper and iron usually is constant, but occasionally copper fails to respond to a fall in iron. One such occurrence is nephritis. One of our patients with chronic nephritis had 30.95 mg. of iron per hundred cubic centimeters of whole blood and a blood copper content of 0.180 mg. This was a normal response. However, as the disease progressed and the anemia became more severe, the iron content fell to 22.05 mg. but the copper content failed to rise; it dropped to 0.145 mg. In another female patient with chronic nephritis, the iron content of the blood was 33.9 mg. per hundred cubic centimeters and the copper content 0.123 mg. These figures represent a hypoferronemia without a hypercupremia. If much albumin is present, more copper is excreted in the urine.

In a splenectomized patient the copper content occasionally fails to respond to a drop in iron, but this seems temporary and as the patient adjusts himself to his splenectomy normal values soon occur. The function of the spleen in copper metabolism is not well understood. It is one of the chief storehouses for copper, but other than this no definite function in copper metabolism can yet be assigned to the spleen.

9. Sachs, A.; Levine, V. E.; Griffith, W. O., and Hansen, C. H.: Copper and Iron in Human Blood: Comparison of Maternal and Fetal Blood After Normal Delivery and After Cesarean Section, Am. J. Dis. Child. **56**:787 (Oct.) 1938.

FUNCTION OF IRON

There are four forms of iron, namely, hemoglobin iron, plasma iron, easily split off iron and nuclear iron. The hemoglobin contains the largest share of iron, and its function is well known. The plasma iron or serum iron is the transport iron, which Moore and his co-workers have so ably described.[10] They have shown that the values for plasma iron and serum iron are practically the same and hence have called the serum iron the transport iron. The easily split off iron was well described by Barkan[11] and was so termed because weak acids free it from its chemical combinations in erythrocytes and in plasma. Its function is not definitely known. The nuclear iron is comparable to the iron found in practically all cells and is part of the respiratory enzyme mechanism.[12]

The functions of iron in man are manifold, but there are five interesting phases in which blood iron participates, namely storage of iron, catalysis, ferrification, production of hemoglobin and transportation of iron.

Storage.—Iron is stored chiefly in the liver, spleen, bone marrow and kidneys but is found in all cells of the body. The amount of iron in the human body varies with the age, sex, size and nutritional state of a person. A large share of the body's iron is found in the circulating blood. A normal adult has about 85 cc. of blood per kilogram of body weight.[13] A male adult who normally has 50 mg. of iron per hundred cubic centimeters of blood would have 3 Gm. of circulating iron, while a female adult of similar weight with normally 45 mg. per hundred cubic centimeters of blood would have only 2.7 Gm. of circulating iron. Chang and Harrop[14] found the circulating blood volume between 63 and 76 cc. per kilogram of body weight. This figure was arrived at by the carbon monoxide method, which yields lower values than the dye method.

The approximate total iron content of an average adult according to Fowler[15] is 4.5 Gm. The largest part, about 2.5 Gm., is in the circulating hemoglobin. The second largest amount, about 1.3 Gm., is in the available store bases. The third portion is found in the nuclei and cytoplasm of all types of cells in the body, which is not available for use in hemoglobin regeneration. When the red cells which have completed their life cycle are destroyed in the spleen or elsewhere, the hemoglobin released is broken down into globin, bile pigment and iron. This iron is the major source of the body's iron supply.

Catalysis.—Warburg's establishment of the respiratory ferment as an iron complex[12] has been a stimulus to the study of metallic catalysts and enzymes. The chromatin in the nucleus of every cell contains iron. The nuclear material dominates the metabolism of the cell. The ferruginous portion of hemoglobin, the heme, has

10. Moore, C. V.; Quiligan, J. J., Jr., and Read, J. T.: The Chemical Methods and Normal Values for Plasma Iron and "Easily Split-Off" Blood Iron, J. Clin. Investigation **15**:613 (July) 1937. Moore, C. V.; Doan, C. A., and Arrowsmith, W. R.: The Mechanism of Iron Transportation: Its Significance in Iron Utilization in Anemic States of Varied Etiology, ibid. **15**:627 (July) 1937.

11. Barkan, G.: Ueber das leicht abspaltbare Bluteisen und sein Verhältnis zum Hämoglobin, Ztschr. f. physiol. Chem. **148**:124, 1925.

12. Warburg, O.: Enzyme Problem and Biological Oxidations, Bull. Johns Hopkins Hosp. **46**:431 (June) 1930.

13. Keith, N. M.; Rowntree, L. F., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

14. Chang, N. C., and Harrop, G. A., Jr.: Determination of Circulating Blood Volume with Carbon Monoxide, J. Clin. Investigation **5**:393 (April) 1928.

15. Fowler, W. M.: Iron Deficiency Anemias, J. Omaha Mid-West Clin. Soc. **2**:16 (Jan.) 1941.

been shown to be closely related to respiratory enzymes and to various undetermined substances in animal cells. This relationship demands attention because of its bearing on transportation and interchange of iron in the organism.

Ferrification.—This term is used to denote deposition of iron in inflammatory areas. The mobilization and deposition in areas of inflammation have been described fully by Menkin,[16] and she has advanced a definite protective function for iron in tuberculous lesions. Iron accelerates growth of connective tissue cells, a fact which suggests that it may aid in tissue repair. Excessive deposits of iron in various types of hepatic cirrhosis are also accompanied by fibrosis.[17]

Hemoglobin Production.—Iron is one of the most essential parts of the hemoglobin molecule and is the most important factor in iron deficiency anemias.

Iron Transportation.—The serum iron is the transport iron and has been previously mentioned. The exchange of iron between the circulating blood and the tissue cells is still an unsolved problem. It is known that very little of the absorbed iron is excreted and most of it is conserved and reutilized.

FUNCTIONS OF COPPER

The functions of copper are not as clearly understood as those of iron. Copper acts as a catalyst with reference to growth, respiration and hemopoiesis.

Growth.—The earliest function assigned to copper was that of a promoter of growth. This was found in its relationship to plants. Copper increased the growth of plants unless present in too concentrated amounts, in which case it inhibited growth.[18] Rats maintained on a diet rich in copper showed a greater increase in weight than those on a diet restricted as to copper.[19]

The liver of the embryo and that of the newborn animal of most species contain higher percentages of copper than the liver of the adult of the same species.[20] In man [21] the same is true, and this high percentage of copper in the fetal liver is necessary so that its storehouses will not be depleted during the first few months of infancy, when the diet may be low in copper. This fact was demonstrated in the figures previously shown during pregnancy.[22] The mother is constantly trying to fill the liver of the fetus with copper in order to prepare it for its early life.

Respiration.—Copper plays an important role in the respiratory process of certain crustaceans and mollusks. Hemocyanin is the respiratory pigment of these animals. Copper bears the same relationship to hemocyanin as iron does to hemoglobin and is present in about the same proportion.[23] Copper accelerates

16. Menkin, V.: Studies on Inflammation; Fixation of Metal in Inflamed Areas, J. Exper. Med. **51**:879 (June) 1930; Accumulation of Iron in Tuberculous Areas, Am. J. M. Sc. **185**:40 (Jan.) 1933.

17. Sachs, A., and Russum, C.: Hemochromatosis, Nebraska M. J. **22**:121 (April) 1937.

18. Allison, R. N.; Bryan, O. C., and Hunter, J. H.: Bulletin 190, Florida Agricultural Experiment Station, 1927.

19. Flinn, F. B., and Inouye, J. M.: Some Physiological Aspects of Copper in the Organism, J. Biol. Chem. **84**:10 (Oct.) 1929.

20. Cunningham, I. J.: Some Biochemical and Physiological Aspects of Copper in Animal Nutrition, Biochem. J. **25**:1267, 1930.

21. Morrison, D. B., and Nash, T. P., Jr.: Copper Content of Infant Livers, J. Biol. Chem. **88**:479 (Sept.) 1930.

22. Sachs, Levine and Fabian.[1b] Sachs, Levine, Griffith and Hansen.[9]

23. McCollum, E. V.; Orent-Keiles, E., and Day, H. G.: The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 211.

oxidation of iron.[24] The oxidation of glutathione is accomplished by the action of copper, whereas iron and other metals fail in this capacity.[25]

Hemopoiesis.—Copper seems essential to hemopoiesis, although it is not part of the hemoglobin molecule. Stein and Lewis [26] have definitely shown it to be an important factor in erythropoiesis. Elvehjem and his co-workers have shown what an important part it plays in hemoglobin formation, namely, that of a catalyst. We have demonstrated that copper is an essential element in hemopoiesis because in any type of anemia copper is called forth to mobilize iron from the storehouses, as evidenced by its rise in the whole blood when iron falls. This is especially well shown in bleeding experiments on dogs and likewise in massive hemorrhage from bleeding peptic ulcers.

Copper is transported in the plasma or serum the same way as iron. We have demonstrated in our experiments on dogs that oral administration of copper sulfate is followed by a substantial increase in the copper in the blood serum, as is shown by figure 4.

The dogs were made to fast for eighteen hours, after which we established a basal copper level in the serum from hour to hour for seven hours. The fasting

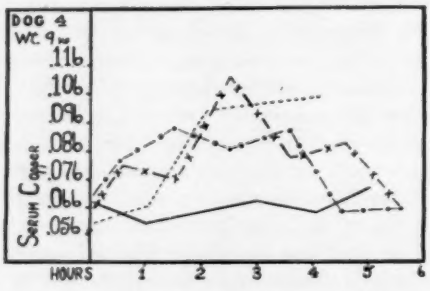

Fig. 4.—Rise in serum copper (expressed in milligrams per hundred cubic centimeters) following oral administration of copper sulfate. Solid line indicates basal level; broken line with x's, values after a dose of 2 mg. of copper sulfate per kilogram; broken line with circles, values after a dose of 8 mg. of copper sulfate per kilogram; broken line, values after a dose of 16 mg. of copper sulfate per kilogram.

values for serum copper remained practically constant. Different doses of copper sulfate were used, 2, 8 and 16 mg. per kilogram of body weight. The dogs retained the 2 and the 8 mg. doses but vomited after the 16 mg. dose. All showed a definite rise in the copper content of the blood serum.

Our experiments with administration of copper to human beings are not completed at this time but will be reported later. Our averages of copper and iron in whole blood and in serum of normal males and females are shown in table 1.

Our recent analyses of the copper and iron content of whole blood and serum of 10 normal men and 10 normal women are shown in tables 2 and 3. These

24. Quartaroli, A.: Il binomino ferro-rame in chimica e in biologia, Ann. di chim. applic. **22**:517, 1932.

25. Voegtlin, C.; Johnson, J. M., and Rosenthal, S. M.: Catalytic Action of Copper in Oxidation of Crystalline Glutathion, Pub. Health Rep. **46**:2234 (Sept. 18) 1931.

26. Stein, H. B., and Lewis, E. C.: Stimulating Action of Copper on Erythropoiesis, J. Nutrition **6**:465 (Sept.) 1933.

determinations were made with the photoelectric colorimeter. Our previous analyses of copper and iron in whole blood were made by colorimetric methods, previously described.

TABLE 1.—*Comparison of Average Values* of Copper and Iron in the Blood of Normal Males and Females*

Sex	Whole Blood Copper	Whole Blood Iron	Serum Copper	Serum Iron
Males	0.132	50.0	0.084	0.154
Females	0.131	45.0	0.098	0.139

* Expressed in milligrams per hundred cubic centimeters.

TABLE 2.—*Determinations* of Iron and Copper in the Blood of Normal Male Adults*

Name	Age	Red Blood Cell Count	Hemoglobin, Gm. per 100 Cc.	Serum Iron	Serum Copper	Whole Blood Copper	Whole Blood Iron
1. Hils	20	4,800,000	13.1	0.168	0.076	0.105	44.0
2. Hasl	21	5,216,000	14.8	0.127	0.087	0.098	49.6
3. Arch	22	5,760,000	16.8	0.162	0.086	0.090	56.4
4. Fitz	22	5,984,000	14.8	0.181	0.071	0.100	49.6
5. Dem	23	5,504,000	16.3	0.192	0.080	0.094	54.8
6. Addi	23	4,896,000	13.4	0.147	0.089	0.109	45.2
7. Gabr	24	4,864,000	14.9	0.176	0.104	0.101	50.0
8. Ande	25	5,408,000	15.2	0.118	0.080	0.100	51.2
9. Egan	25	5,408,000	15.2	0.107	0.070	0.103	51.2
10. Dew	27	5,472,000	16.8	0.159	0.084	0.106	56.4
Average	23	5,331,000	15.1	0.154	0.084	0.102	50.8
Range	20 to 27	4,800,000 to 5,984,000	13.1 to 16.8	0.107 to 0.192	0.070 to 0.104	0.090 to 0.109	44.0 to 56.4

* Expressed in milligrams per hundred cubic centimeters.

TABLE 3.—*Determinations* of Iron and Copper in the Blood of Normal Female Adults*

Name	Age	Red Blood Cell Count	Hemoglobin, Gm. per 100 Cc.	Serum Iron	Serum Copper	Whole Blood Copper	Whole Blood Iron
1. Dobe	20	4,448,000	13.9	0.069	0.089	0.104	46.8
2. Lark	21	4,992,000	14.0	0.190	0.124	0.121	47.2
3. Marc	22	4,576,000	13.4	0.100	0.088	0.105	45.2
4. Vaug	23	4,864,000	12.7	0.108	0.104	0.108	42.8
5. Arkr	23	4,672,000	13.3	0.181	0.100	0.107	44.8
6. Hick	23	4,672,000	13.9	0.168	0.108	0.102	46.8
7. Tull	24	4,200,000	14.3	0.182	0.092	0.105	48.0
8. Hugh	25	4,480,000	13.4	0.122	0.078	0.101	44.0
9. Shep	25	4,384,000	13.4	0.125	0.098	0.114	44.0
10. Jenn	28	4,544,000	12.4	0.140	0.100	0.106	41.6
Average	23	4,583,000	13.5	0.129	0.098	0.107	45.1
Range	20 to 28	4,200,000 to 4,992,000	12.4 to 14.3	0.069 to 0.190	0.078 to 0.124	0.101 to 0.121	41.6 to 48.0

* Expressed in milligrams per hundred cubic centimeters.

The iron content of serum as well as of whole blood is lower in females than in males. The copper content of serum and of whole blood is relatively high in females. This is in accord with the relative anemic tendency reflected in all female bloods.

ABSORPTION OF IRON AND COPPER

Moore and his co-workers [27] have shown that iron is absorbed chiefly in the duodenum, to some extent in the jejunum and to a lesser extent in the ileum. They did their work in human beings by use of the Miller-Abbott tube. We have performed experiments on absorption of iron in isolated loops in dogs and have corroborated their findings on absorption. Iron was absorbed in the upper and middle jejunal loops but very slightly in the distal loop. We also investigated absorption of copper. Copper was absorbed in the upper jejunal loop, but practically not at all in the middle and distal loops.

The Thiry fistula loops were made in all dogs, and the technic used was as follows:

With intratracheal ether anesthesia and with the usual sterile precautions, the abdomen was opened through a midline incision about 4 inches (10 cm.) long. The first loop of the jejunum was identified, and about 2 feet (60 cm.) of the bowel was marked off with an Allis forceps. This segment of bowel was separated from the remainder of the jejunum, by means of rubber-covered clamps on the part to be anastomosed and a Kocher forceps on the part which was to form the fistula. Continuity of the intestinal tract was restored by end to end

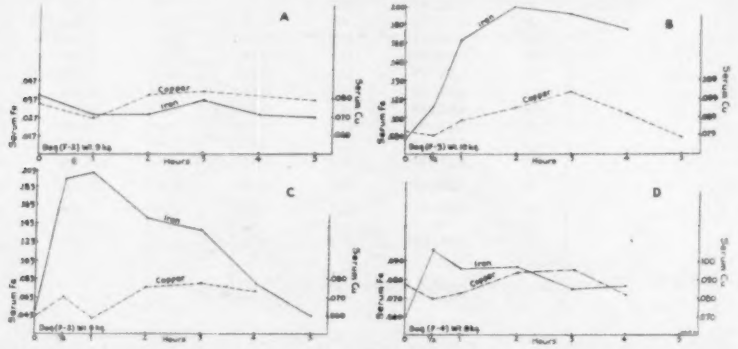

Fig. 5.—Studies of iron and copper in the serum (expressed as milligrams per hundred cubic centimeters). *A*. Relative constancy during a five hour period. *B*. Definite absorption of iron and some absorption of copper from a loop of proximal jejunum, after 3 mg. of ferrous sulfate and 1 mg. of cupric sulfate per kilogram. *C*. Definite absorption of iron and slight or no absorption of copper from a loop of midjejunum, after a dose of 3 mg. of ferrous sulfate and 1 mg. of cupric sulfate per kilogram. *D*. Slight or no absorption of iron and copper from a loop of distal jejunum, after a dose of 3 mg. of ferrous sulfate and 1 mg. of cupric sulfate per kilogram.

suture with two layers of silk. The distal end of the separated loop was closed and inverted over a Kocher clamp, and the other end of the bowel was brought out through a stab wound in the right rectus muscle and was anchored in place by sutures through the peritoneal and outer coat of the bowel. The abdominal incision was closed in layers by the usual method.

Fistulas of this type were made in the upper, the middle and the lower loop of the jejunum in different animals, as illustrated in figure 6.

27. Moore, C. V.; Bierman, H. O.; Minnich, V., and Arrowsmith, W. R.: Studies in Iron Absorption with Special Reference to the Relationship of Iron Metabolism to Ascorbic Acid, in Blood, Heart and Circulation: Symposium, Publication 13, American Association for the Advancement of Science, Washington, D. C., 1940, pp. 34-37. Moore, C. V.; Arrowsmith, W. R.; Welch, J., and Minnich, V.: Studies in Iron Transportation and Metabolism: Observations on the Absorption of Iron from the Gastro-Intestinal Tract, J. Clin. Investigation **18**:543 (Sept.) 1939.

The treatment of iron deficiency anemia is on a more rational basis than in previous years. Iron must be in an ionizable form before it can be absorbed. This is true whether it is in an organic or an inorganic form. The amount of iron required each day varies with age, sex and size of the person. It has been estimated that 5 to 15 mg. of iron constitutes the daily requirement. Different authors have reported various amounts, but these seem to be the most frequently

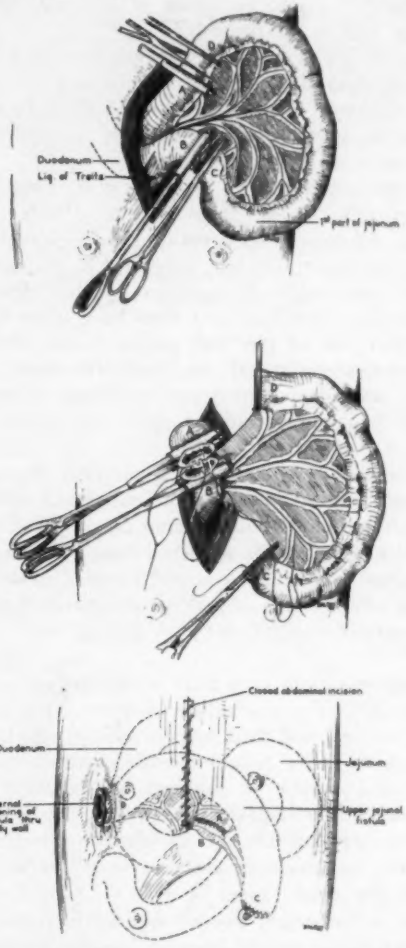

Fig. 6.—Drawings illustrating technic of making Thiry fistula loops in dogs.

quoted figures. They are based on very carefully performed balance studies by Fowler [15] and his associates. Iron is excreted largely in the bile, feces and urine.

The figures reported for the daily requirements of copper have not been as widely accepted as the figures for iron. Some authors set the daily amount at 2 mg. Chou and Adolph [28] maintained that the copper intake should be 2 mg.

28. Chou, T. P., and Adolph, W. H.: Copper Metabolism in Man, Biochem. J. **19**:476, 1935.

a day for adults. Sherman [29] likewise gave 2 mg. of copper as the daily needs. Other authors stated that a 70 Kg. man requires 7 mg. of copper per day.[30] Some give the daily needs of children to be 0.6 mg. of available iron and 0.1 mg. of copper per kilogram of body weight.[29]

Copper is mostly excreted in the feces and urine. The most iron and copper that is lost is usually lost by hemorrhage. The adult body is said to contain from 100 to 150 mg. of copper.[29] With an intake of 2.17 mg., the excretion through the bowel was 1.22 mg. and in the urine 0.27 mg.[29]

A great controversy exists as to whether copper is or is not needed in addition to iron to combat certain types of anemia. Most clinicians have found it unnecessary to add copper. We have never found a copper deficiency in analyses of the blood that we have made and do not feel that added copper is needed in the treatment of iron deficiency anemias.

Copper is present in abundance in liver, oysters, nuts and legumes and is present in varying quantities in all types of food. Water, milk and all other liquids contain copper. All iron pharmaceutic products contain copper. Dust contains variable amounts of copper. In fact, it is hard to get copper-free materials to prevent contamination with copper in analyses for that element. It is true that a milk diet is a copper-poor diet, but most diets have more than an ample supply of copper. We feel that one of the best guides to an adequate intake of iron is the rise in the reticulocyte count. Moore stated that when using this as a guide he has never found a secondary reticulocyte response or any evidence of more rapid regeneration of hemoglobin after copper was added than was obtained by iron alone.[31]

The nutritional anemias of infants are a problem that needs further study before one can definitely say whether or not copper is needed. In the cases we have been privileged to examine we have found no copper deficiency to date.

The ferrous salts are more readily absorbed than the ferric salts. Hydrochloric acid seems of great value in ionizing iron and hence in making it more available. Iron must be available whether it is organic or inorganic. Foods vary from 20 per cent for some leafy vegetables to 100 per cent for egg yolks in availability of iron supply.

The calcium-phosphorus ratio may have some bearing on absorption of iron. Phosphorus interferes with the absorption of iron experimentally, and calcium can prevent this interference and thus assures efficient utilization of iron. Clinically this as yet seems to be of little importance with adequate diets. Absence of free hydrochloric acid cannot be supplied by the addition of dilute hydrochloric acid, but nature accommodates itself to its needs, as is readily seen in patients with idiopathic hypochromic anemia who have no free acid.

Infections, diarrheas or deficiency diseases may interfere with absorption of iron. Hemorrhage is the chief cause for loss of iron. Growth demands more iron both for increase in the supply needed and for increase in the blood volume. Pregnancy needs careful observation because greater demands are present and the fetus must be adequately supplied. Twin pregnancies and premature infants demand close attention because the supplies may not be adequate.

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29. Harrow, B.: Text Book of Biochemistry, Philadelphia, W. B. Saunders Company, 1940.

30. Conferences on Therapy [from Cornell University Medical School and New York Hospital]: Treatment of Blood Disorders; The Use of Iron and Other Metals, J. A. M. A. **114**:2301 (June 8) 1940.

31. Moore, C. V., in Round Table Discussion on the Therapeutics of Anemia, J. Pediat. **17**:554 (Oct.) 1940.

When iron is prescribed it must be noted whether the patient actually takes it; otherwise the therapeutic results will prove perplexing. Many patients claim that they are taking the medication but in reality are not. Persons may react differently and better to one form of iron than to another. Ferrous salts are most easily absorbed.

It is claimed that lack of vitamin B_6 can produce anemia,[31] but at present the application of this vitamin to the treatment of anemia is in the experimental stage. Expensive products containing liver extract, vitamins, copper and iron are of no more value than simple ferrous sulfate. If a vitamin deficiency does exist, the amount of vitamin administered in expensive preparations may not be adequate to cover the deficiency. Occasionally liver extract in adequate doses given with iron seems to have value and should be used. The use of cobalt has been recommended, but as yet its employment therapeutically has been too limited to permit an opinion relative to its efficiency.

When iron is given, it must be ascertained that it is being absorbed and is producing an adequate hemopoietic response. If this response is insufficient, the reasons must be sought. The two most important reasons for failure of iron therapy in anemia are continued hemorrhage and infection. Some anemias, however, do not respond to treatment, and no satisfactory explanation can be found for such failures.

Creighton University School of Medicine.

ANEURYSM OF THE HEART

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Although aneurysm of the heart has been recognized for almost two centuries, it is only recently that the antemortem diagnosis has been made with any assurance. The advent of more thorough study of patients with heart disease by roentgenologic methods has considerably increased the frequency with which the correct diagnosis is made. The first account of aneurysm of the ventricle was by Galeati[1] in 1757, but the first detailed description of the condition was given by Matthew Baillie[2] in 1793. Since then, from time to time, other papers have appeared dealing with the subject. These have been fully reviewed by Hall,[3] Sternberg[4] and Parkinson, Bedford and Thomson,[5] who added cases of their own. The first case in which the condition was diagnosed by means of roentgen rays was reported by Sézary and Alibert[6] in 1922. Since then, in many of the cases reported it has been recognized by roentgen study, although the diagnosis is still difficult, as is shown by the fact that in 1926 Pletnew,[7] in a summary of 300 cases previously described, found that in only 6 had the correct diagnosis been made ante mortem. Gradually definite criteria by which the condition can be ascertained are being evolved; so it seems probable that an increasing number of cases will become recognized.

Aneurysm of the ventricular septum is usually diagnosed only post mortem; hence, in this study only aneurysms affecting the ventricular walls will be considered. It is possible that a septal aneurysm might produce the Bernheim syndrome or, if extensive, that enlargement of the heart might be seen on roentgen examination. However, there are so many conditions which frequently cause enlargement of the heart that diagnosis of septal aneurysm is unlikely to be made.

The following 13 cases, in 9 of which the diagnosis was proved by autopsy, are reported because there was well marked aneurysmal dilatation of the ventricular wall. In 4 of the group in which autopsy was performed the diagnosis was made ante mortem, and 3 patients are still alive. One patient presented undisputable clinical evidence of the condition, but permission for an autopsy could not be obtained.

REPORT OF CASES

CASE 1.—F. A., a white man aged 64, was admitted to the Brooklyn Hospital on June 28, 1935, suffering from severe precordial pain. A diagnosis of acute coronary occlusion was made. The infarct was situated in the anterior wall of the left ventricle. In October of this year he was readmitted to the Brooklyn Hospital, suffering from acute heart failure (left side). In February 1936 he was admitted to Kings County Hospital. He stated that he had been dyspneic, that since his illness in 1935 he had had dull precordial pain, which was gradually

From the Department of Medicine, Long Island College of Medicine, and the Kings County and Long Island College hospitals.

1. Galeati, D. G., cited by Parkinson, Bedford and Thomson.[5]
2. Baillie, M.: The Morbid Anatomy of Some of the Most Important Parts of the Human Body, London, J. Johnson, 1793.
3. Hall, D. G.: Edinburgh M. & S. J. **14**:322, 1903.
4. Sternberg, M.: Das chronische partielle Herzaneurysma, Leipzig, Franz Deuticke, 1914.
5. Parkinson, J.; Bedford, D. E., and Thomson, W. A. R.: Quart. J. Med. **7**:455, 1938.
6. Sézary, A., and Alibert, T.: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:172, 1922.
7. Pletnew, D. D.: Ztschr. f. klin. Med. **104**:378, 1926.

becoming worse, and that he had had edema of the ankles for two months. These symptoms continued in varying degree throughout the remainder of his life. He was admitted to the hospital on eleven different occasions (nine times to the Brooklyn Hospital and twice to Kings County Hospital). In 1936 a visible heaving pulsation was noted (at the Brooklyn Hospital), and in June 1937 a definite diagnosis of aneurysm of the left ventricle was established by roentgen examination. In October 1937 the physical examination revealed that he was suffering from cardiac decompensation. The pulse rate was 84 beats per minute and the blood pressure 108 systolic and 82 diastolic. There was a marked precordial pulsation, separate from the apex beat, in the third intercostal space. There was no thrill. The heart sounds were diminished, and there was a systolic murmur at the apex. The lungs showed bilateral pleural effusion, and there was edema of both ankles. The Wassermann reaction was negative. The electrocardiogram was of the type associated with previous infarction in the anterior wall of the left ventricle. The roentgenogram showed enlargement of the left ventricle. Along the upper part of the lateral border of the heart there was a bulge about 5 cm. in diameter. On fluoroscopic examination there was marked systole by expansion of the sac. This was also demonstrated by kymographic examination. The patient died on Oct. 10, 1939, at the Brook-

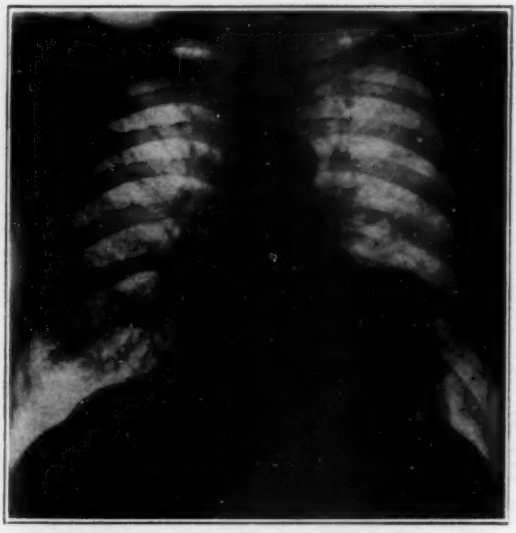

Fig. 1 (case 1).—Aneurysmal bulge at the upper part of the left border.

lyn Hospital, and the autopsy, performed by Dr. Arnold deVeer, showed an aneurysm of the anterior surface of the left ventricle about 6 cm. in diameter, the superior margin of which was 3 cm. from the auriculoventricular sulcus. There was also a small aneurysmal bulging in the posterior wall of the left ventricle, to which a large thrombotic mass was adherent. The anterior descending branch of the left coronary artery was occluded slightly above the site of the aneurysm, but the circumflex branch and the main right coronary were patent. Branches of the right coronary artery supplying the posterior wall were thrombosed. Death was due to acute hemorrhagic pancreatitis from embolization to the pancreaticoduodenal artery. There was a large recent infarct in the spleen.

Case 2.—A. J., a Negress aged 13,[8] was admitted to the cardiac clinic of Kings County Hospital in January 1938, complaining of cough and palpitation of six months' duration. The previous history showed nothing of note, and there was no history of syphilis in either the parents or child. Physical examination showed a well developed young girl who appeared in good condition. The pulse was regular in rhythm, at a rate of 96 beats per minute, and the

8. This case has been reported in detail previously (Hollander, A. G., and Crawford, J. H.: Am. Heart J. **20**:762, 1940).

blood pressure was 132 systolic and 92 diastolic. There was a marked visible pulsation over the lower portion of the precordium between the sternum and the nipple. No thrill was felt. There was a soft systolic murmur at the apex. With each heart beat a clicking sound was also heard in the region of the apex. The results of physical examination were otherwise normal, as were those of laboratory studies. The Wassermann reaction was negative. The electrocardiogram showed a negative T wave in lead I and an almost absent R wave in lead IV (right arm wire connected to precordial electrode and left leg wire to left leg electrode). A roentgenogram showed a localized bulge about the midportion of the left border of the heart. Fluoroscopic and roentgenokymographic examinations showed systolic expansion in the region of the bulge. A diagnosis of aneurysm of the heart was made. The patient continued to be active with no particular complaints. While playing in a school playground on Aug. 28, 1940, she suddenly fell over, dead. Autopsy showed a heart of normal size. Projecting from the septum of the mitral ring between the auricle and ventricle directly beneath the posterior cusp of the mitral valve was a multiloculated sac, measuring 5 by 7 cm. This consisted of dense fibrous tissue in which on microscopic examination strands of heart muscle were seen.

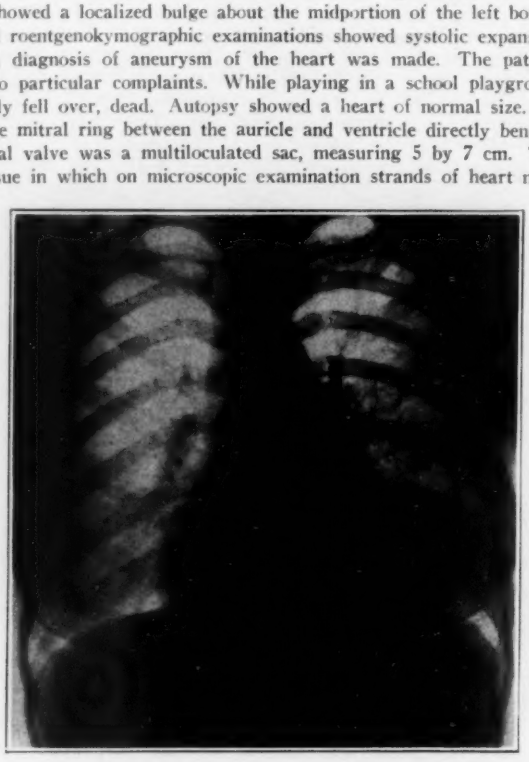

Fig. 2 (case 2).—Aneurysmal bulge in the midportion of the left border.

The adjacent auricular and ventricular muscle was normal except for the presence of recent Aschoff bodies. There were no old rheumatic lesions, and the coronary vessels were normal.

CASE 3.—J. S., a Negro aged 46, was admitted to Kings County Hospital on Sept. 22, 1937. Ten days before admission he had been stabbed over the heart. He did not faint, vomit or spit up blood. He continued to work for six days, and then dyspnea, cough and edema of the ankles developed, which gradually increased. Previous to this the patient had always been in good health. On physical examination he was suffering from orthopnea and cough. There was marked bilateral distention of the veins of the neck. The pulse was regular, at a rate of 88 beats per minute, and the blood pressure was 140 systolic and 100 diastolic. There was evidence of the stab wound in the fourth interspace over the cardiac area. The heart was slightly enlarged to the left. A systolic thrill extending from the third interspace to the sternum was felt, and a harsh systolic murmur was heard in the same region. There was no abnormal pulsation noticed. The lungs were filled with dry and moist rales, and the liver was enlarged 3 fingerbreadths. There was marked edema. The Wassermann reaction was 4 plus. The electrocardiogram showed negative T waves in leads II and III. On roentgen examination only some enlargement of the left ventricle was seen. On the following day the temperature rose to 101 F. and the pulse rate to 100 beats per minute. After this the

temperature remained normal. The patient's general condition gradually improved. On October 10 it was noted that a localized pulsation had developed in the region of the stab wound which was not synchronous with the apex beat. There was a marked thrill in this area, and systolic and diastolic murmurs were heard all over the precordium, the site of maximum intensity being in the area of pulsation. There was no Corrigan pulse. At this time the electrocardiogram showed a diphasic T wave in lead II and a negative T wave in lead III, while roentgen examination showed no change from the previous study. Despite this, it was felt that a diagnosis of traumatic aneurysm of the heart could be made. The patient was discharged from the hospital on November 21 with no evidence of heart failure.

CASE 4.—J. M., a white man aged 65, was admitted to Kings County Hospital on Sept. 3, 1941. He had had a hemiplegia of the left side nine years before, from which he had made a satisfactory recovery. He then felt well until 1938, when he was seized one day with severe pain in the chest, lasting two to three days. This was accompanied by diarrhea and hiccup. After that time he had dyspnea on exertion, which varied in severity, but there was no recurrence of precordial pain. He had severe dyspnea when he walked and also severe nocturnal dyspnea. The legs felt as if they were paralyzed. Physical examination

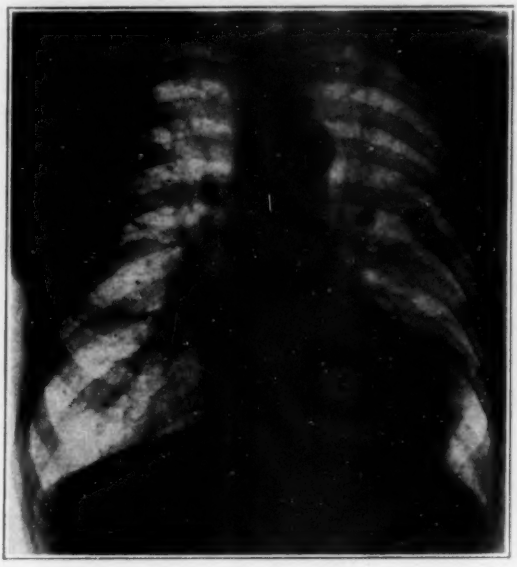

Fig. 3 (case 4).—Aneurysmal bulge on the left border slightly below the middle.

revealed a thin man with slight cyanosis of the lips. There was marked generalized arteriosclerosis. The pulse was regular, at a rate of 88. The blood pressure was 132 systolic and 82 diastolic. There was a diffuse forcible pulsation in the region of the fourth, fifth and sixth interspaces. It was maximum in the fifth space but covered a wide area, extending as far as the midaxillary line at the level of the fifth interspace. No thrill was felt over the pulsation. The heart sounds over the pulsation were of fairly good quality, but at the base of the heart they were faint. There was a systolic murmur over the pulsation. Gallop rhythm was not present. There were bilateral basal rales in the lungs. The liver was not enlarged. There was weakness of the left leg, and a Babinski sign could be elicited on this side. The Wassermann reaction was negative. The electrocardiogram showed a negative T wave in lead I. In lead IV the R wave was absent; the S wave was slurred and the RS-T segment was elevated, being followed by a slightly negative T wave. Roentgen examination showed calcification of the aorta and a localized bulge just above the apex. The heart was not significantly enlarged. Fluoroscopic examination showed a marked saccular dilatation of the left ventricular wall, just above the apex. There was a vigorous pulsation in this area, and the pulsations were opposite to those of the rest of the ventricle. The patient was discharged, improved.

Case 5.—J. C., a Negro aged 43, was admitted to Kings County Hospital on May 28, 1937, complaining of dyspnea and of swelling of the legs and abdomen. The former had been present for a long time, but the latter had developed recently. There was a history of rheumatic fever at the age of 15. Physical examination showed some distention of the veins in the neck and considerable edema. The pulse rate was 90 beats per minute, and the blood pressure was 140 systolic and 100 diastolic. The heart was considerably enlarged, but there were no murmurs and the heart sounds were good. There were rales at the bases of both lungs, and the liver was enlarged 4 fingerbreadths. The Wassermann reaction was 4 plus. The electrocardiogram showed slurring of the QRS segment in all leads and a negative T wave in lead I. A roentgenogram was not taken at this time. The patient was discharged after the heart failure was relieved. He was readmitted on March 20, 1939, suffering from acute bronchopneumonia, from which he recovered. On May 9 and October 27 he returned with heart failure and had similar physical findings. On the latter admission roentgen examination revealed a heart which was enlarged to the left. About halfway on the left ventricular contour there was angulation, and below this, flattening of the wall. Roentgenokymographic examination showed systolic expansion in this region. In December he suffered from an attack of hemiplegia of the left side, from which he made a satisfactory recovery. He was readmitted on Jan. 26, 1940, again with heart failure. The final admission was March 3, 1941, for the same complaints. The only significant changes which had taken place were that the electrocardiogram now showed left bundle branch block and the blood pressure was 170 systolic and 120 diastolic. On March 7 pain developed in the suprapubic region and nausea but there was no vomiting. There were tenderness in this region and some rigidity. Shortly after this he died. Autopsy revealed a heart which was considerably enlarged. There was concentric hypertrophy of the left ventricle. The apex was replaced by fibrous tissue, and there was an aneurysmal dilatation in this region. The coronary vessels were markedly sclerotic, but no occlusion was found. Cardiac cirrhosis of the liver was present and an old thrombus in the right femoral artery. Death was due to mesenteric thrombosis with peritonitis.

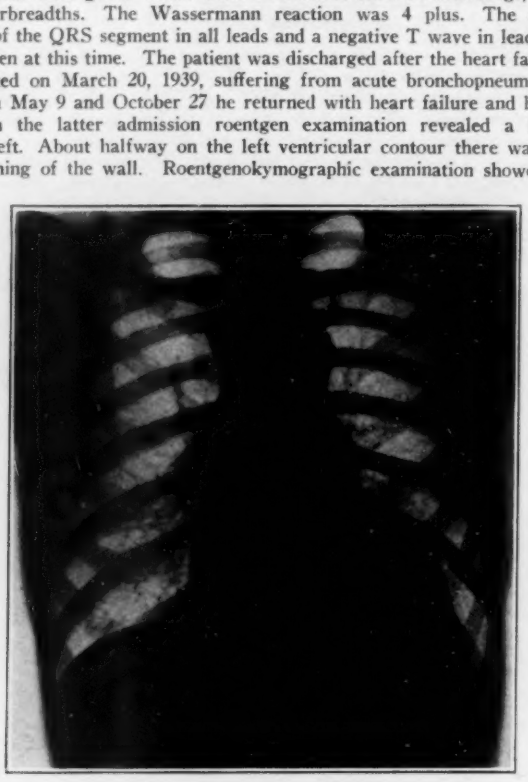

Fig. 4 (case 5).—Angulation of the left border of the heart. The aneurysm was proved by autopsy to be in the lower part of the anterior wall of the left ventricle and apex, the flattened area.

Case 6.—A. D., a white man aged 58, was admitted to Kings County Hospital on Jan. 22, 1941. He stated that he had had high blood pressure for a long time. Seven days before

admission he had suffered intermittent precordial pain. On the day of admission he was seized with extremely severe pain in the chest, which did not abate. Physical examination showed a man in severe pain. The heart rate was 96 beats per minute, and the blood pressure was 162 systolic and 90 diastolic. The heart did not appear enlarged, and there was a soft systolic murmur at the apex. The Wassermann reaction was negative. The electrocardiogram showed a typical coronary occlusion of the Q_1 T_1 type. The patient made a satisfactory recovery and was discharged on March 11, 1941. He was readmitted on September 15. He stated that he had had no precordial pain since discharge but had suffered from increasing dyspnea on exertion, which had been worse in the last week; otherwise, he had no complaints. On physical examination there was generalized arteriosclerosis. The pulse rate was 72 beats per minute, and the blood pressure was 154 systolic and 94 diastolic. The apex was clearly visible in the sixth interspace in the anterior axillary line. Above and separate from this, over a wide area in the fourth and fifth interspaces, extending as far as the mid-axillary line, there was a diffuse pulsation. This seemed to start before and to last longer than the apical thrust. There was no thrill felt. The heart sounds were good. A systolic murmur

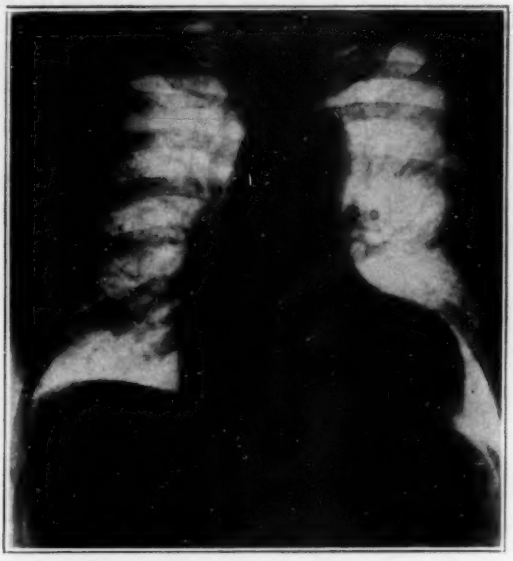

Fig. 5 (case 6).—Angulation of the left border. The aneurysm was shown by fluoroscopic and roentgenokymographic study to be in the region of the flattened area.

was heard at the apex, but this was less intense over the upper pulsation. There was a faint systolic murmur at the aortic area. There were some dry rales at the base of each lung. The electrocardiogram was similar to that on discharge previously. The roentgenogram showed angulation of the left border, the lower part being flat. In this area on fluoroscopic examination there was seen some bulging during systole, but the pulsations were diminished. This was confirmed by roentgenokymographic examination. After a short stay the patient was discharged much improved.

Case 7.—M. M., a white man aged 59, was admitted to the Brooklyn Jewish Hospital on May 20, 1936. He suffered from acute coronary occlusion, the electrocardiograms being of the Q_3 T_3 type. He improved satisfactorily and was discharged on July 21. Immediately after this he took a considerable amount of exercise one day and on returning home had severe dyspnea and dull precordial pain. He was readmitted to the Jewish Hospital on July 23. The pulse rate was 120, and the blood pressure was 140 systolic and 80 diastolic. The heart was enlarged to the left, and there was a marked diffuse heaving over the entire precordium. The heart sounds were faint, and a systolic murmur was present at the aortic area. There was

evidence of fluid in both pleural cavities. The patient was transferred to Kings County Hospital on July 30. The pulse rate had fallen to 80, and the blood pressure was 150 systolic and 90 diastolic. The apex was in the sixth space, 1 inch (2.5 cm.) outside the midclavicular line. The heart sounds were faint. There were moist rales at the bases of the lungs, but the fluid in the pleural cavities had disappeared. Roentgen examination showed an angulation of the left border of the heart with suggested myomalacia in the lower part of the left ventricle and apex. Fluoroscopic examination showed diminished pulsation in this region with some systolic expansion, and kymographic studies confirmed this. The Wassermann reaction was negative. The patient was discharged after he recovered from the attack but was readmitted on September 30, with the same symptoms. At this time the diffuse pulsation which had been noted over the whole precordium seemed to be most pronounced at the apex. On October 3 the electrocardiogram suggested that he had had a recent, as well as an old, infarction. The patient remained free from signs of decompensation while at rest, but any activity brought on heart failure. He was transferred to the Jewish Home for Incurables, where he died this summer. An autopsy was not obtained.

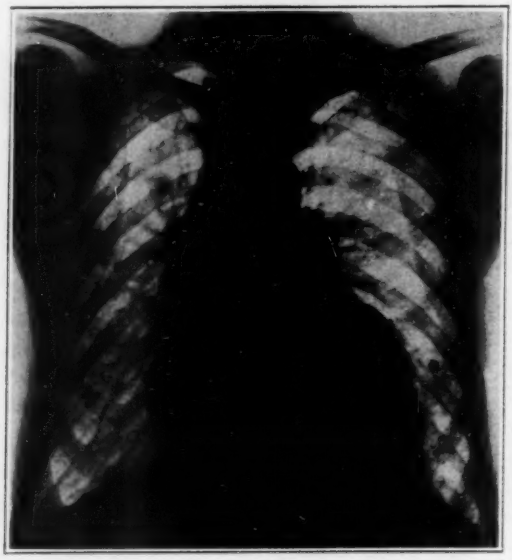

Fig. 6 (case 7).—Angulation of the left border. The aneurysm was demonstrated by fluoroscopic and roentgenkymographic study to be in the region of the flattened area.

Case 8.—J. K., a white man aged 62, was admitted to Kings County Hospital on Aug. 20, 1937. He stated that two weeks before, while he was eating, severe abdominal pain suddenly developed. This was situated near the umbilicus and radiated to the left upper quadrant. There were no gastrointestinal symptoms except that he had had diarrhea for two days. He also suffered from some dyspnea. He continued to work, but the pain and dyspnea continued. The pain was most severe when he lay down. The condition grew progressively worse; so he came to the hospital. Physical examination showed pronounced orthopnea. The respiratory rate was 40 per minute. The veins in the neck were distended. The pulse was weak, but the rhythm was regular, at a rate of 115 beats per minute. The blood pressure was 184 systolic and 112 diastolic. The heart was enlarged to the left, and the heart sounds were faint. No murmurs were heard. There were bilateral basal rales, and the liver was enlarged 3 fingerbreadths. The electrocardiogram suggested an acute coronary occlusion with the infarct in the anterior wall of the left ventricle. Roentgen examination showed generalized enlargement of the heart with dilatation of the aorta. The Wassermann reaction was negative. On November 3 he had what appeared to be a cerebral embolus, and a week later he died. Autopsy showed a considerably enlarged heart. The pericardium was adherent to the left ventricle. In the region of the apex there was an aneurysm 8 cm. in diameter filled with

antemortem thrombus. There were an old occlusion of the anterior descending branch of the left coronary artery and severe generalized coronary sclerosis. There was no evidence of recent infarction. Generalized arteriosclerosis was found, and there was blood-tinged fluid in the right pleural cavity. The liver was enlarged 3 fingerbreadths.

Case 9.—C. G., a white man aged 55, entered Long Island College Hospital on Jan. 6, 1934. He stated that until three weeks before he had never been sick. At this time he noticed edema of the ankles in the evening. After a week the swelling had extended farther up the legs. At about the same time he noticed pain of a gripping nature on both sides of the chest radiating to the left shoulder. The pain was not related to exercise. He also began to cough and had chilly sensations. He suffered from shortness of breath, which became progressively worse. The night before his admission nocturnal dyspnea was present, accompanied by precordial pain. The temperature on admission was 100.4 F., and the pulse was regular at a rate of 84 beats per minute. The blood pressure was 110 systolic and 80 diastolic. There was cyanosis of the lips and extremities and edema of the legs. The heart was enlarged downward and to the left. A systolic crunching sound was present in the midprecordium. There were no murmurs. There were an impaired percussion note at both bases and many rales on both sides. The liver was enlarged 2 fingerbreadths. The Wassermann reaction was negative. The electrocardiogram showed evidence of coronary occlusion. On roentgen examination, the heart was seen to be enlarged in all diameters, and there was calcification of the aorta. On the patient's second day in the hospital tachycardia at rate of 150 beats per minute developed. He was given digitalis and quinidine, and the next day the previous rate was resumed. On January 15 auricular fibrillation was observed but his general condition had improved. The fibrillation continued, but then he commenced to lose ground. On January 30 a strong irregular cardiac impulse was seen and felt between the ribs and iliac crest. He was stuporous and died that evening. Autopsy revealed a considerably enlarged heart. The pericardium was adherent to the apex. The lower segment of the left ventricle was the seat of a large aneurysm, and there were old and recent infarctions in this area. There was an adherent thrombus in the region of the aneurysm. An old occlusion of the left anterior descending artery was present, and sclerosis of the other coronary vessels. An embolus was present in the left cerebral artery.

Case 10.—H. A., a white man aged 71, was admitted to Long Island College Hospital on Dec. 18, 1939. He stated that for about eight years he had suffered from bronchitis with cough and sputum. He was dyspneic for about three to four years and had some edema of the ankles for three months. Physical examination showed a slightly dyspneic man. The pulse was regular in rhythm, at a rate of 80 beats per minute, and the blood pressure was 92 systolic and 64 diastolic. The heart was considerably enlarged, the apex being in the anterior axillary line. There were a short systolic murmur at the apex and a rough systolic murmur at the aortic area. There were scattered dry rales in the lungs, and the edge of the liver was just palpable. The Wassermann reaction was negative. The electrocardiogram showed changes suggestive of an old anterior infarct. The patient was discharged on December 31 much improved. He was readmitted on May 24, 1941. He had been comparatively well since discharge until two weeks before, when congestive heart failure again developed. At this time the pulse rate was 104 beats per minute and the apex was in the midaxillary line. There were many moist rales in both lungs. The liver was enlarged 4 fingerbreadths. His condition became progressively worse, and he died the next day. Autopsy showed a considerably enlarged heart. In the region of the apex and the anterior wall along the septum there was an aneurysmal dilatation about the size of a child's fist. It contained antemortem thrombus, and the pericardium was adherent in this area. There was an old occlusion of the anterior descending branch about the junction of the upper and middle thirds. The rest of the coronary vessels showed moderate sclerosis.

Case 11.—E. T., a white man aged 77, was admitted on Oct. 30, 1932 to the ear, nose and throat service of Long Island College Hospital, suffering from acute suppurative mastoiditis. The pulse rate was 78 beats per minute and the temperature 100 F. The blood pressure was 158 systolic and 92 diastolic. The heart was not significantly enlarged. There was a harsh systolic murmur at the apex and a softer systolic murmur at the aortic area. The results of physical examination were otherwise normal. The Wassermann reaction was negative. The mastoid condition became progressively worse, and on November 2 an operation was performed. The condition continued to deteriorate, and the patient died on November 7. Autopsy revealed some enlargement of the heart. On the posterior surface of the left ventricle, close to the region of the mitral valve, there was a calcified aneurysm of the left ventricle. The sac contained no antemortem clot. There was calcification of the aortic valve, with stenosis. The anterior descending artery showed calcification and was narrowed 1 cm. from its origin. There was moderate sclerosis of the right coronary artery. There were two aneurysms of the aorta near the origin of the iliac vessels, measuring, respectively, 5 by 7 cm. and 5 by 6 cm. The right kidney was atrophied.

CASE 12.—R. S., a white woman aged 58, was admitted to Kings County Hospital on Dec. 19, 1938. One week before, severe precordial pain radiating down the left arm and dyspnea had developed. This improved, but the pain again returned severely the day before admission. Physical examination revealed a woman suffering from some dyspnea. The temperature was 100 F., and the pulse was regular in rhythm, at a rate of 115 beats per minute. The blood pressure was 130 systolic and 74 diastolic. The heart was enlarged to the left, and there were systolic murmurs at the apex and aortic areas. The lungs were normal, and the liver was not enlarged. The Wassermann reaction was negative. The electrocardiogram showed a QRS segment of low voltage in all the standard leads; the R wave was almost absent, and there was an elevated RS-T segment in lead IV, suggesting an acute infarction of the anterior wall. No roentgenogram was taken. The condition progressed satisfactorily, but on December 29 the patient suddenly became comatose. Her pulse became irregular, and she died soon after. Autopsy showed an enlarged and dilated heart. On the anterior surface of the left ventricle at the apex there was a large gray-white aneurysmal bulge, to which the pericardium was adherent. There were marked coronary sclerosis and arteriosclerosis of the aorta. Acute pancreatitis was present.

CASE 13.—J. T., a white man aged 53, was admitted to Kings County Hospital on April 25, 1941. His condition was so serious that no history could be obtained. The temperature was 106 F., and the respiratory rate was 44. The blood pressure could not be obtained. Extreme enlargement of the right cervical glands was present. The heart was totally irregular, at a rate of about 140 beats per minute. It was enlarged, and the heart sounds were weak. No murmurs were heard. The lungs were normal, and the liver was not enlarged. The Wassermann reaction was negative. A bedside roentgenogram was taken and apart from cardiac enlargement showed nothing significant. An electrocardiogram was not obtained. The patient died soon after admission. Autopsy revealed considerable cardiac enlargement. The pericardium was adherent to the lower half of the left ventricle. At the apex there was an aneurysmal dilatation, 6 by 5 cm. The wall was hard and calcified, and there was no evidence of muscle in this region. The aortic and mitral valves were sclerotic. The coronary arteries were very sclerotic, but no occlusion was found. Marked generalized arteriosclerosis was present.

ETIOLOGY

All authors agree that in the majority of cases cardiac aneurysm follows coronary occlusion. Sternberg [4] stated that in 84.8 per cent of the 207 cases which he analyzed cardiac aneurysm followed coronary occlusion. In 13 of the 16 cases of Parkinson, Bedford and Thomson [5] there was a previous coronary occlusion. The evidence of coronary occlusion consists of either a typical history or positive electrocardiographic signs or both. In 8 of the present series of cases there were the characteristic signs of a previous occlusion. Cases have been described in which in patients with infective endocarditis the aneurysm followed abscesses of the ventricular wall caused by infected emboli. A few cases have been described in which the cardiac aneurysm was secondary to gummas of the ventricle. Two patients in the present series who had no evidence of a previous coronary occlusion had a positive Wassermann reaction, but postmortem examination of 1 showed no syphilitic lesions in the heart muscle while in the other the aneurysm was secondary to trauma. Congenital aneurysms have been reported in rare instances. These have mainly involved the pars membranacea septi. In 1 of the aforementioned cases the aneurysm, projecting from the ventricular wall, was of congenital origin. Trauma of the heart is sometimes followed by aneurysm and was the cause in 1 of this series. Necrosis of the myocardium secondary to rheumatic lesions has been stated to be an etiologic factor but must be very infrequent. In 1 case of undetermined origin there was a history of rheumatic fever at the age of 15 but the autopsy gave no evidence that this played any part; no satisfactory cause could be determined.

A summary of the literature shows that 66 per cent of the patients with this condition are males. In the present group there were 11 men and 2 women.

CLINICAL FEATURES

Site.—Most aneurysms occur in the left ventricle, as is to be expected since myocardial infarction of the right ventricle is uncommon. The most frequent site is the apex and its immediate vicinity, and the artery which has been most often occluded is the anterior descending branch of the left coronary artery. In 9 cases of the present series the aneurysm was located in the region of the apex; in 3, higher on the anterior or lateral wall, and in 1, on the posterior wall.

Symptoms.—There are no symptoms characteristic of aneurysm of the heart; indeed, the patient may be able to carry on ordinary activity without discomfort and the aneurysm may be discovered during the course of a routine examination (case 2). The most common symptoms are those associated with congestive heart failure, although in some instances angina pectoris may be the sole complaint.

Physical Signs.—The most important physical sign is the presence of abnormal pulsation in the precordial area. It is stated that a displaced apex which is more diffuse than normal and both forceful and heaving is characteristic. This is, however, frequently seen in large hearts without aneurysm and would be valuable only if the possibility of aneurysm were considered as a result of other evidence. It was seen in 2 cases in the present series. Libman and Sacks,[9] Libman[10] and Dressler and Pfeiffer[11] stressed the value of a pulsation separate and distinct from the apex, especially when it is situated above the fifth rib. This is a most important sign, and its presence frequently permits the diagnosis to be made by physical examination alone. It was seen in 5 of my cases. Sometimes the abnormal pulsation appeared before the apical thrust and lasted longer. A muffling of the heart sounds or a disproportion between the forcefulness of the pulsation and the intensity of the heart sounds has been described. This was found in only 3 of my patients. Some had heart failure and might have shown it without aneurysm. Furthermore, the heart sounds are often diminished after coronary occlusion even when no aneurysm is present. Gallop rhythm has been noted in the literature but was not noted in these cases. It also may be evidence of myocardial failure and is not characteristic of aneurysm. Lutembacher[12] stressed the value of pain over the apex. This was found in 1 of my patients but does not seem to be a sign of any particular value. Percussion demonstrates only a very large aneurysm and has been superseded by roentgen examination. Murmurs do not aid in the diagnosis. A systolic murmur is often present, and 1 of my patients had a double murmur over the abnormal pulsation. The blood pressure was not significantly elevated except in 1 instance. Congestive heart failure was present at some time in 9 of my cases and is the common cause of death.

ROENTGENOLOGIC OBSERVATIONS

The most valuable information is obtained by fluoroscopic examination, because one can study not only the cardiac contour from all angles but the pulsations as well. Roentgenograms should be taken for detailed analysis not only in the posteroanterior position but in the oblique position, the most favorable position having been determined by fluoroscopic study. Certain aneurysms of the anterior wall and those on the posterior wall can be seen only in roentgenograms taken with the patient in the oblique position. By roentgenokymographic examination

9. Libman, E., and Sacks, B.: Am. Heart J. **2**:321, 1927.
10. Libman, E.: Proc. Interstate Post-Grad. M. A. North America (1926), 1927, p. 60.
11. Dressler, W., and Pfeiffer, R.: Ann. Int. Med. **14**:100, 1940.
12. Lutembacher, R.: Arch. d. mal. du cœur **13**:49, 1920.

one is enabled to study the pulsations in detail. Studies after the injection of diodrast may demonstrate the aneurysm clearly if it is not filled with thrombus.

Parkinson, Bedford and Thomson [5] described the following signs as the most important aids in establishing the diagnosis by roentgenography: (1) enlargement of the left ventricle with deformity of its contour, (2) a localized protuberance inseparable from the shadow of the heart on rotation of the patient, (3) abnormal or absent pulsation of the aneurysmal zone, (4) evidence of adhesions between the heart and the wall of the chest or the diaphragm and (5) calcification of the wall of the sac or its contained clot. They particularly stressed the value of an abrupt ledging of the anterior contour of the heart as seen with the patient in the right oblique position. Aneurysms of the posterior wall are demonstrated with the patient in the left oblique position and sometimes cause displacement of the esophagus.

Three of the patients in the present series had no roentgen examination, as cardiac aneurysm had not been suspected clinically. Eight showed enlargement of the heart and 3 a localized bulge. Angulation of the left ventricular contour was seen 3 times. Abnormal pulsations demonstrated by fluoroscopic or roentgenokymographic examination are frequently of the greatest value. Their character varies from a reversal of the normal type to absent pulsation. Schwedel and Gross [13] stated that in their cases the pulsations were synchronous, asynchronous, systolic or contrapulsile. The pulsations were proved to be abnormal in the aneurysmal zone in 6 of my patients. Of these, 4 showed an expansion during systole of the rest of the ventricle, with ballooning out in a most striking manner in 2 of them; the other 2 had very small or no pulsations. In none were pulsations of the normal type. Gross and Schwedel [14] have emphasized the value of localized pericardial adhesions in the diagnosis. This was not present in any of my cases, but on autopsy adhesions of the pericardium to the sac were seen in 6; they were absent in 1, and in 2 there was no note as to its presence or absence. None of the patients in this study showed calcification of the wall of the sac or of a thrombus contained therein. When calcification is seen it must be differentiated from calcification of the pericardium. The latter is on the surface and usually more diffuse, while in calcification of an aneurysm the calcification should be localized and not confined to the surface.

ELECTROCARDIOGRAPHY

Eliaser and Konigsberg [15] described electrocardiographic signs which they considered of diagnostic value in cases of cardiac aneurysm. In none of my cases were there changes of this type. Electrocardiograms were of help only when they established the existence of a previous coronary occlusion.

PROGNOSIS

Cardiac aneurysm indicates, as a rule, very extensive damage to the ventricle. It has been suggested that aneurysm is more likely to develop when an adequate period of rest has not followed the coronary occlusion. This seems a reasonable expectation, but at least several of my patients were known to have received very satisfactory treatment of the occlusion. Nine of them had heart failure at some time during their course. However, it was surprising in many instances to observe

13. Schwedel, J. B., and Gross, H.: Am. J. Roentgenol. **41**:32, 1939.
14. Gross, H., and Schwedel, J. B.: New York State J. Med. **41**:488, 1941.
15. Eliaser, M., and Konigsberg, J.: Electrocardiographic Findings in Cases of Ventricular Aneurysm, Arch. Int. Med. **64**:493 (Sept.) 1939.

the extent of the recovery which ensued and how much the patient was able to accomplish despite the presence of an aneurysm. Indeed, in case 2 (congenital aneurysm) there were no cardiac symptoms at all. This feature has been commented on by other authors. The aneurysm itself does not seem to play a great part in determining the outcome in most instances; the deciding factor seems to be the functional capacity of the rest of the ventricle. Rupture of the heart was not a cause of death in any of my cases. The usual termination is progressive cardiac decompensation. In some instances fatal embolization takes place.

DIFFERENTIAL DIAGNOSIS

1. *Tumor of the Heart.*—As in aneurysm, this may cause a bulge on the cardiac contour. If the tumor is metastatic, there may be evidence of carcinoma elsewhere, while there is, as a rule, no evidence of a previous coronary occlusion. With a tumor the heart is not enlarged usually, whereas with an aneurysm this is common. The pulsation in a solid tumor is synchronous with the rest of the heart, whereas in an aneurysm there is usually systolic expansion or absent pulsation. In a soft tumor, such as a very vascular sarcoma or a hemangioma, a reversal of pulsation may take place. Fulton [16] described a case of systolic expansion which responded well to antisyphilitic therapy.

2. *Aneurysm of a Sinus of Valsalva.*—This may project to the left and upward and thus cause difficulty. A positive Wassermann reaction or aortic insufficiency would suggest this as a likely diagnosis.

3. *Aneurysm of a Coronary Artery.*—This type of aneurysm is rare and seldom large. If it reaches a sufficient size to be easily seen, it may readily be mistaken for an aneurysm of the heart.

4. *Aneurysm of the Descending Aorta.*—This condition may be seen projecting to the left of the cardiac contour, but careful roentgenologic study will easily establish the correct diagnosis.

5. *Diverticulum of the Pericardium, Loculated Pericardial Effusion or Cyst of the Pericardium.*—Any of these conditions may resemble aneurysm. Cushing [17] found on a review of the literature that the first in most instances was seen on the right side, where aneurysms are not common, and he also stated the belief that a change in shape of the shadow on respiration is an important diagnostic feature. The history of a previous pericarditis may help in differentiating effusion, and the type of pulsation seen in aneurysm may be an aid. Differences in density of the roentgenographic shadow between the heart and the pericardial disease may at times help to settle the matter.

6. *Enlarged Pulmonary Conus.*—An enlarged pulmonary conus secondary to mitral stenosis, congenital heart disease, cor pulmonale or Ayerza's disease should give little difficulty in differential diagnosis, as in these the results of roentgenographic examination rarely simulate aneurysm and the clinical features of these diseases are characteristic.

7. *Tumors of the Chest.*—Tumors of the mediastinum or of the lung can be separated by careful roentgenologic study and the clinical features of pressure in the mediastinum or evidence of pulmonary disease.

8. *Para-Apical Pad of Fat.*—The para-apical pad of fat is easily differentiated from an apical aneurysm by roentgen examination.

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16. Fulton, M. N.: Aneurysm of the Ventricle of the Heart, J. A. M. A. **116**:115 (Jan. 11) 1941.

17. Cushing, E. H.: Diverticulum of Pericardium, Arch. Int. Med. **59**:56 (Jan.) 1937.

COMMENT

One of the most striking features noted in reviewing the literature is the marked increase in the incidence of cardiac aneurysm in recent years compared to the incidence in earlier reports. These were based on autopsy studies; hence it seems that the condition was unlikely to have been overlooked. In 1884 Legg [18] observed only 3 instances in 1,890 autopsies. Summaries of large series of postmortem studies showed as low, if not a lower, incidence. In contrast, Parkinson, Bedford and Thomson,[5] combining their own statistics with those of other authors reporting its occurrence after coronary occlusion, stated that cardiac aneurysm takes place in 9 per cent. Coronary occlusion was not usually recognized before its description by Herrick [19] in 1912; hence it is difficult to say whether or not there has been an increase in its incidence. However, there is such a marked discrepancy that such would hardly account for the difference. The most likely explanation is that the earlier authors considered as instances of aneurysm only those cases in which there was a definite bulging of the ventricle beyond the general contour of the heart, whereas of late less marked changes have been so diagnosed. Even small indentations of the endocardial wall at the site of an old infarct, when the epicardial surface was not involved, have been reported as aneurysms in some series. This seems hardly warranted. If such are to be included, one would say that in most instances where an area of myomalacia is present an aneurysm exists. Gubner and Crawford,[20] by roentgenokymographic examination, demonstrated that systolic expansion of the infarcted area takes place in a large percentage of cases of coronary occlusion. Similar observations have been reported after fluoroscopic study by Master, Gubner, Dack and Jaffe.[21] It would seem better to confine the term "cardiac aneurysm" to a permanent localized bulging or, during systole, a well marked localized expansion beyond the contour of the rest of the heart. On fluoroscopic examination one sometimes sees a localized bulging of the wall during systole which during diastole collapses so that the wall of the heart is flattened. Christian and Frik [22] reported such a case. The diagnosis was made by roentgen examination, but the aneurysm was incorrectly located, as autopsy revealed that what had been thought to be the aneurysm was the normal part of the ventricle. Figures 4, 5 and 6 illustrate this condition, while figures 1, 2 and 3 show permanent localized bulging. In considering the pulsations of the ventricle one would expect that every instance in which a large part of the myocardium has been damaged would show bulging during systole with marked reversal of pulsation. The reason for this not being so is that it may be prevented by mural thrombi, reenforcement by strong pericardial adhesions or by calcification.

There is no doubt that roentgen examination is the most important aid in the diagnosis of cardiac aneurysm, as changes in the contour can be, as a rule, clearly delineated. Unfortunately, the most common site for aneurysm is the apex, which is the position in which the contour can be studied least effectively. At this point the heart and diaphragmatic shadows mingle, which tends to obscure deformities of the cardiac contour. A diffuse concentric apex rounding or a broadened blunted apex has been stated to be characteristic. These are, however, so frequently seen in patients suffering from hypertension or aortic insufficiency, which are relatively

18. Legg, J. W.: Some Account of Cardiac Aneurysms, London, J. & A. Churchill, 1884.
19. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.
20. Gubner, R., and Crawford, J. H.: Am. Heart J. **18**:8, 1939.
21. Master, A. M.; Gubner, R.; Dack, S., and Jaffe, H. L.: Proc. Soc. Exper. Biol. & Med. **41**:89, 1839.
22. Christian and Frik: Klin. Wchnschr. **1**:582, 1922.

common conditions, that it is very doubtful whether a satisfactory differentiation can be made. Zdansky [23] points out that aneurysm must attain a considerable size before a clearly circumscribed bulging at the apex is seen. The apex region can be studied in more detail during very deep inspiration or after inflation of the stomach with gas. Aneurysms higher in the ventricular wall or on the posterior wall, the latter being usually basal, can be visualized much more readily.

CONCLUSIONS

1. There are no symptoms characteristic of aneurysm of the heart. It may be asymptomatic, but as a rule some symptoms due to congestive heart failure are present. Sometimes angina pectoris is the only complaint.

2. The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are: (*a*) a history or electrocardiographic proof of previous coronary occlusion; (*b*) the presence of an abnormal precordial pulsation distinctly separated from the apex pulsation, particularly when it is situated above the fifth rib; (*c*) on roentgen examination a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen or an angulation of the left border of the heart; (*d*) systolic expansion in the region of the abnormality as seen on fluoroscopic or roentgenokymographic examination, which is practically conclusive evidence, and small contractions or none in this area, which are strongly suggestive; (*e*) localized pericardial adhesions or calcification of the aneurysmal wall or its contents.

3. The following conditions simulate aneurysm of the heart most closely and must be carefully differentiated from it: (*a*) tumor of the heart; (*b*) aneurysm of a sinus of Valsalva; (*c*) aneurysm of a coronary artery; (*d*) calcification of the pericardium; (*e*) diverticulum of the pericardium; (*f*) loculated pericardial effusion; (*g*) cyst of the pericardium.

The physicians of Kings County and Long Island College hospitals who had some of the patients reported on under their care at different times gave permission to include their cases in the series. The physicians of Brooklyn Hospital gave permission to use the data for the patient admitted to that institution (case 1).

178 Eighth Avenue.

23. Zdansky, E.: Röntgendiagnostik des Herzens und der grossen Gefässe, Berlin, Julius Springer, 1939.

ENTEROCOCCIC INFECTIONS

AN EVALUATION OF THE IMPORTANCE OF FECAL STREPTOCOCCI AND RELATED ORGANISMS IN THE CAUSATION OF HUMAN DISEASE

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That streptococci having distinctive properties are normally present in the contents of the human bowel and that these organisms may at times be the etiologic agents of infectious processes in man was first emphasized by Andrewes and Horder [1] in 1906, who applied the descriptive term Streptococcus faecalis to them. Since that time a considerable literature has grown up dealing with various aspects of the classification of the fecal streptococci and organisms closely related to them, all of which have come to be included in a loosely defined group, the enterococci.

Very recently the development by Lancefield [2] of a precipitin technic has permitted a more satisfactory classification of the hemolytic streptococci than had previously been possible, and it is now known that nearly all serious human infections, particularly those of the respiratory tract, are caused by members of her group A.[3]

Sherman has demonstrated that most of the streptococci of the human bowel [4] are serologically homogenous and are members of the Lancefield group D. Furthermore, he has described biologic tests [5] which permit the satisfactory classification of these streptococci in the absence of serologic studies and has pointed out that both hemolytic and nonhemolytic varieties occur which are serologically and biologically identical.

In the light of these recent important observations, the interpretation of the earlier work on the fecal streptococci becomes difficult, since many of the differential tests used are now known to be unreliable. This is especially true in relation to organisms isolated from and described as the etiologic agents in human infections. For this reason it is unprofitable to review the literature dealing with enterococcic infections in man other than to point out that these organisms have long been recognized to be occasionally the cause of bacterial endocarditis and to be frequently isolated from infections of the urinary tract. No comprehensive description of the types of disease produced by fecal streptococci is available, nor any estimate of the frequency with which they may be recovered from clinical

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1. Andrewes, F. W., and Horder, T. J.: A Study of the Streptococci Pathogenic for Man, Lancet **2**:708, 775 and 852, 1906.

2. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Streptococci, J. Exper. Med. **57**:571, 1933.

3. (*a*) Rantz, L. A., and Keefer, C. S.: The Distribution of Hemolytic Streptococci, Groups A, B, and C in Human Infections, J. Infect. Dis. **68**:128, 1941. (*b*) Hare, R.: Sources of Haemolytic Streptococcal Infection of Wounds in War and Civil Life, Lancet **1**:109, 1940.

4. Sherman, J. M.: The Enterococci and Related Streptococci, J. Bact. **35**:81, 1938.

5. (*a*) Sherman, J. M.: The Streptococci, Bact. Rev. **1**:1, 1937. (*b*) Graham, M. C., and Bartley, E. O.: Some Observations on the Classification of the Enterococci, J. Hyg. **39**:538, 1939.

materials. A few observers have discussed the importance of the enterococci in general terms,[6] but they have presented few specific clinical data. It is now particularly important that the clinical significance of the enterococci be established, since these organisms have been repeatedly shown to be almost completely resistant to the bacteriostatic action of sulfonamide compounds.[7] The use of these agents in infections caused by fecal streptococci may not be followed by a satisfactory clinical result.

A study was therefore undertaken in this clinic of hemolytic and nonhemolytic streptococci isolated from human clinical materials, modern clinical and biologic methods being applied in their classification. The detailed results of these observations have been described elsewhere.[8] Of great interest was the fact that nearly one half of the streptococci recovered from sources other than the respiratory tract were enterococci.

It is the purpose of this paper to describe the disease processes from which these streptococci were isolated, to discuss the results of chemotherapy and to define, in general, the place of the enterococci in clinical medicine.

IDENTIFICATION OF THE ENTEROCOCCI

The enterococci occur in the tissues and in culture as lancet-shaped, gram-positive cocci, usually in pairs or very short chains. They resemble pneumococci so closely in appearance that special studies are necessary to differentiate them. In liquid mediums growth is very rapid and diffuse. On blood agar plates the colonies are large, flat, smooth and gray. Beta hemolysis will frequently be present, although the typical Str. faecalis is entirely nonhemolytic.

The important biologic characteristics, as described by Sherman,[5a] which permit the identification of the enterococci are the ability of these bacteria to grow well at 10 C. and 45 C. in the presence of 6.5 per cent sodium chloride, 0.1 per cent methylene blue and a p_H of 9.6 and to resist heating for thirty minutes at 60 C. The last-mentioned qualification has been most widely applied in the past and is now known to be inadequate for the differentiation of the fecal from other kinds of streptococci.

Practically all of the streptococci which fulfil these biologic requirements will be found serologically to be members of the Lancefield group D. Approximately 25 per cent of the strains isolated from human sources will be hemolytic, and 10 per cent will be found to liquefy gelatin. For the purpose of clinical investigation it is most profitable to consider the hemolytic, nonhemolytic and proteolytic strains as members of a very closely related group of streptococci rather than as separate species, since no difference in the type of disease process caused by each variety has been demonstrated.

The technical and statistical details of the biologic and serologic classification of the streptococci have been described elsewhere.[8] From these observations it appears that a streptococcus which grows well in 6.5 per cent sodium chloride broth and in milk containing 0.1 per cent methylene blue may be safely classified

6. Houston, T.: Enterococci. Proc. Second Internat. Cong. Microbiol., 1936, p. 141. Aschoff, L.: Ueber den Enterokokkus (Streptococcus Libman), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 87.

7. Neter, E.: (*a*) The Bacteriostatic Action of Sulfanilamide upon Hemolytic and Non-Hemolytic Enterococci, J. Bact. **40**:383, 1940; (*b*) Experimental Observations on Bacteriostatic Action of Sulfanilamide and Related Compounds upon Enterococci, with Particular Reference to Strains Isolated from Urinary Tract Infections, J. Urol. **45**:241, 1941.

8. Rantz, L. A.: The Serological and Biological Classification of Streptococci from Human Sources, J. Infect. Dis. **71**:68 (1942).

as an enterococcus for clinical purposes without recourse to the more elaborate biologic and serologic methods. All of the organisms isolated from human beings which are described in this report grew at 10 C. and 45 C. in the presence of 6.5 per cent sodium chloride and 0.1 per cent methylene blue. Half were studied serologically and demonstrated to be members of group D, including nearly all of those from sources other than the urinary tract.

SOURCE OF MATERIAL

Enterococci have been isolated from various materials obtained from more than 200 persons during this study. Adequate observations were available in 145 cases from the clinic services of Stanford University Hospitals and have been selected for study. They are presented under several classifications, according to the site of the infection, as is shown in table 1.

Respiratory Tract.—Extensive studies of the normal flora of the nasopharynx have revealed that hemolytic members of group D are very rarely present.[9] Nonhemolytic varieties are probably also uncommon.[10] No instances of pharyngitis or pneumonia have been observed during the period of observation included in this report in which enterococci could be definitely implicated as etiologic agents. Hemolytic enterococci were isolated as the predominant organisms in 1 case of

TABLE 1.—*Distribution of Cases by Site of Infection*

Source	Number of Cases
Respiratory tract infections	8
Cardiovascular infections	3
Abdominal infections	23
Urinary tract infections	105
Miscellaneous infections	6
Total	145

chronic purulent sinusitis of 50 examined. Cultures were positive on four occasions over a period of four months. No specific therapy other than the irrigation of the sinuses was undertaken.

It is evident that enterococci are present at times in the nasopharynx, since in 6 cases they were isolated in pure culture from the pus obtained on the paracentesis knife used to perform a myringotomy for acute purulent otitis media. Five strains were nonhemolytic, and 1 was hemolytic. That these streptococci were the cause of the suppurative process seems definite. During the interval in which these cases were studied, 53 other instances of otitis media caused by streptococci were observed. In every case a member of the Lancefield group A was isolated. Enterococci are therefore responsible for approximately 10 per cent of all streptococcic infections of the middle ear. This fact is of interest and attests the greater invasiveness of these organisms over that of the other nonhemolytic and alpha hemolytic streptococci constantly present in the nasopharynx.

This enterococcic otitis media may well be contrasted clinically with the more frequent type caused by streptococci of group A. All of the patients were infants, the average age being 10 months and the extremes 4 and 15 months. Group A infections were observed in children with an average age of 4.5 years, with extremes of 10 months and 11 years, only 20 per cent being less than 2 years of age.

9. Rantz, L. A.: The Hemolytic Streptococci: Observations on the Carrier State in the San Francisco Area, J. Infect. Dis. **69**:248, 1941. Hare.[8b]

10. Safford, C. E.; Sherman, J. M., and Hodge, H. M.: Streptococcus Salivarius, J. Bact. **33**:263, 1937.

The infectious process was bilateral in 2 instances and unilateral in 4, the same ratio as for group A infections. The onset in both groups almost invariably occurred after an infection of the upper respiratory tract. Treatment was instituted in all 6 cases on the first or second day of illness and consisted of myringotomy and use of the ear washes and nose drops. No sulfonamide compounds were administered. On this regimen 4 patients (66 per cent) recovered completely in an average of twelve days. Fifty-seven per cent of 33 patients with group A infections similarly treated recovered in an average of twenty-five days. Two of the 6 with enterococcic infections of the ear were treated, after twenty-one days of conservative observation, with sulfanilamide, and in the 1 instance in which adequate data are available the disease was immediately arrested. Group A infections similarly treated also responded well, especially if sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) was the drug used.

One other instance of enterococcic involvement of the ear has been described in detail elsewhere [11] but may be reviewed at this time:

CASE 1.—An 18 year old boy had otitis media and mastoiditis, followed by mastoidectomy. At the time of operation an epidural abscess was present but not thrombosis of the lateral sinus. The temperature became elevated postoperatively, and culture of the blood showed nonhemolytic enterococci. Sulfathiazole was administered, and further operative exploration revealed another abscess over the temporal lobes of the brain, which was drained. Cultures of the spinal fluid were sterile. Later several other intracranial abscesses were evacuated, from the contents of each of which enterococci were recovered which were similar to those isolated from the blood. The administration of sulfathiazole was continued, and the patient eventually recovered, after an illness of five months' duration. All of the suppurative areas were subdural, and none penetrated the brain substance.

There can be no question that surgical drainage of these localized collections of purulent material beneath the meninges was necessary for a favorable outcome, and it is impossible to evaluate the role of therapy with a sulfonamide compound in the recovery of this patient. Sulfathiazole was probably not instrumental in controlling the infectious process during the acute phase of the disease when septicemia was present, since improvement followed surgical drainage of purulent collections and was ineffective in the subacute stage.

Enterococci rarely cause pneumonia, sinusitis or pharyngitis, but they occasionally are the etiologic agents in acute suppurative otitis media. This disease, when due to these organisms, usually occurs in infants, in contrast to infections involving streptococci of group A, which are most frequent during early and middle childhood, at the time when other diseases due to hemolytic streptococci are common.

Enterococcic otitis media untreated at the onset by a sulfonamide compound appears to resolve more quickly than do infections caused by members of group A, similarly treated. In some cases, however, chemotherapy or surgical intervention is required, and 1 has been described in which the initial infection of the ear was followed by mastoiditis, sepsis and an abscess of the brain. It is believed that sulfathiazole did not definitely affect the course of the infection.

Cardiovascular System.—Enterococci are important in infections of the cardiovascular system only as etiologic agents in bacterial endocarditis. In a recent review of enterococcic endocarditis, Skinner and Edwards [12] discovered reports of 37 cases of this disease in the literature and added 2 of their own. Description of the etiologic organisms in most of these cases is so meager that it is impossible to determine whether enterococci, according to the criteria of Sherman,[5a] were involved.

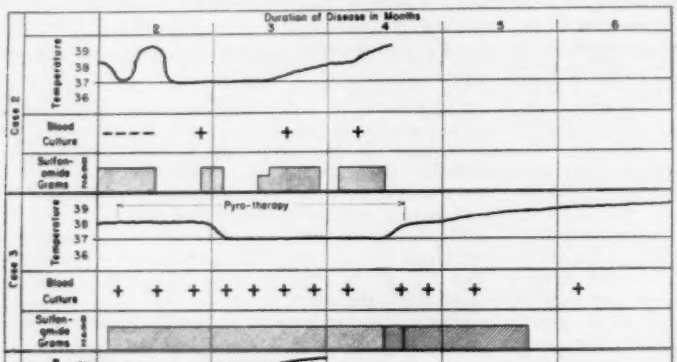
11. Rantz, L. A.: Streptococcal Meningitis, Ann. Int. Med. **16**:716, 1942.

12. Skinner, D., and Edwards, J.: Enterococcal Endocarditis, New England J. Med. **226**:8, 1942.

Twenty per cent of the strains of streptococci recovered in cases of bacterial endocarditis by Moran [13] were enterococci, a value closely approximated during the present study, in which fecal streptococci were isolated in 3 of 16 instances of this disease. These 3 cases will now be described in detail and the clinical and pathologic observations compared with those in 3 published cases [14] in which definite group D enterococci were isolated.

CASE 2.—A 33 year old woman entered the hospital with a complaint of chills and fever for three weeks. Her clinical course is illustrated in the accompanying chart. Attacks of pain in the joints with fever had occurred at 14 and 16 years of age, since which time she had been known to have valvular disease of the heart.

The onset of chills and fever three weeks before the patient's entry to the hospital followed a cold and bronchitis which had persisted during the previous month. Immediately after the



Clinical course of 3 patients with enterococcic subacute bacterial endocarditis.

first chill severe pain had developed in the left flank, and later she had many red painful swellings of the toes and fingers. No petechiae were discovered on physical examination when she was first seen in the hospital, but there were marked clubbing of the fingers and a palpable spleen associated with the frank signs of mitral stenosis and aortic regurgitation. The urine, red blood cell count and hemoglobin were within normal limits, but the total leukocyte count was elevated to 18,000 per cubic millimeter. Culture of the blood gave negative results until the end of the first month in the hospital, after which nonhemolytic enterococci were recovered on several occasions.

Sulfathiazole appeared to control the fever but caused cutaneous eruptions. The substitution of sulfanilamide and later of sulfadiazine failed to alter the course of the disease, and the patient died, after an illness of three and one-half months, with the development of severe precordial pain, many petechiae and a very large spleen.

The anatomic diagnoses were: (1) rheumatic endocarditis of the mitral and aortic valves, (2) subacute endocarditis of the aortic and tricuspid valves, with infectious perforation of the interventricular septum, (3) infarct of the spleen, septic (nonhemolytic streptococcic), and (4) infarct of the kidney (no evidence of focal or diffuse glomerulonephritis).

13. Moran, H.: Classification of Streptococci from Cases of Endocarditis, Proc. Soc. Exper. Biol. & Med. **38**:805, 1938.

14. Williams, C.: Bacterial Endocarditis Due to the Streptococcus Fecalis, Am. Heart J. **18**: 753, 1939. Skinner and Edwards.[12]

CASE 3.—A 26 year old man was admitted to the hospital having suffered chills, fever and night sweats for four weeks. He had always been well, and there was no previous history of any illness resembling rheumatic fever or heart disease. He had had a tooth extracted two months before his entry to the hospital; after this he had not been entirely well but was at work until one month later, when he began to suffer from severe night sweats, malaise and loss of weight, followed by the development of chills and fever. At this time he came to the hospital, and his subsequent course is illustrated in the chart.

On examination he was obviously ill and had fever, but no other abnormalities could be discovered except a soft blowing systolic murmur over the precordium. The results of ordinary laboratory procedures were within normal limits, but the first and eleventh subsequent blood cultures revealed nonhemolytic enterococci. Usually about 100 colonies per cubic centimeter were present.

Continuous treatment with sulfathiazole or sulfadiazine associated with pyrotherapy, the latter being administered on sixteen occasions, failed to alter the course of the disease. The spleen became markedly enlarged and tender and the right hip and shoulder acutely painful, and shortness of breath and precordial pain appeared. The final episode was one which simulated the rupture of an intra-abdominal viscus with the development of an acute diffuse peritonitis. The duration of his illness was five and one-half months.

The anatomic diagnosis was: subacute endocarditis of the mitral valve (no evidence of previous valvular disease), with (*a*) septic infarct of the spleen (nonhemolytic streptococcic), (*b*) rupture of the spleen due to infarct, (*c*) acute peritonitis due to nonhemolytic streptococci, (*d*) multiple abscesses of the heart, (*e*) septic infarct of the kidney (no evidence of glomerulonephritis) and (*f*) septic infarct of the brain.

CASE 4.—A 36 year old woman entered the hospital, pregnant and at term, with a complaint of chills and fever for one month. Her course in the hospital is illustrated in the chart. There was no past history of rheumatic fever or heart disease. The pregnancy, her fifth, had proceeded normally until the last month, when chills and fever supervened and continued until her entry into the hospital without localizing signs or symptoms. On examination she was found to be febrile and the signs of free aortic regurgitation were present, but no other abnormalities could be discovered. She was anemic, the hemoglobin content being only 55 per cent (Sahli); the leukocyte count and the urine were normal, and the first and seven later blood cultures yielded nonhemolytic enterococci.

She was delivered of a normal baby on the seventh day in the hospital. Treatment with sulfapyridine followed by sulfathiazole did not alter the outcome but was associated with a brief return of the temperature to normal. Her spleen became palpable and crops of petechiae appeared, but the urine was always normal. She died after an illness of two months' duration.

The important conditions noted at necropsy were: subacute endocarditis of the mitral and aortic valves (no evidence of previous valvular disease) with subacute myocarditis and acute focal early suppurative hepatitis.

In the 3 cases of enterococcic subacute endocarditis just presented the clinical course was not unlike that of similar infections due to the more common types of alpha hemolytic and nonhemolytic streptococci usually responsible for this condition. Chills, fever, sweats, heart murmurs, splenomegaly, petechiae and other embolic phenomena were regularly present. In some important respects, however, the disease was different. Severe precordial pain occurred in 2 cases, and repeated examination of the urine failed in every case to demonstrate the signs of nephritis so commonly present in subacute bacterial endocarditis.

At necropsy the observations were distinctive. Suppurative lesions were present in the peripheral organs in every case. In 1 only the liver was involved; in another, the myocardium, spleen, kidney and brain, and in the third, only the spleen. In 1 case rupture of a splenic abscess was followed by acute enterococcic peritonitis with death. The extent of these lesions appeared to be roughly correlated with the duration of the illness. Suppuration such as this occurs in approximately 15 per cent of all cases of streptococcic endocarditis [15] but is very rare in other

15. (*a*) Middleton, W. S.: Streptococcus Viridans Endocarditis Lenta, Am. J. M. Sc. **198**: 301, 1939. (*b*) Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Rep. **22**:1, 1926.

than those instances in which enterococci are the cause.[16] Furthermore, no evidence of focal or diffuse glomerulonephritis was discovered at necropsy, also an unusual observation.[15a]

In 2 of the 3 instances, no underlying congenital or rheumatic abnormalities of the heart valves were discovered. Repeated series of observations [15] have shown that in 80 per cent of all cases of subacute bacterial endocarditis some preexisting damage to the endocardium is associated. A review of the 3 previously described cases of definite enterococcic endocarditis shows that in 1 the disease was established on a normal valve; in another extensive peripheral suppuration was present, leading to rupture of the spleen and fatal peritonitis, and in a third extensive amyloidosis was discovered. In none was a focal or diffuse glomerulonephritis observed.

Wallach has previously emphasized [17] the frequency with which suppurative infarction may occur in enterococcic endocarditis and has also described focal myocardial lesions associated with cardiac failure. These appear to be no more than a variation of the generalized suppurative process, since in 1 of the cases described in this report frank myocardial abscesses were found.

It is possible to say, in summary, that enterococcic endocarditis probably tends to occur in persons with normal heart valves more frequently than do other forms of streptococcic infection of the endocardium. Suppuration in the myocardium and in the organs peripheral to the heart occurs uniquely in enterococcic endocarditis and has twice led to splenic rupture and fatal peritonitis. Focal and diffuse glomerulonephritis have been conspicuous by their absence.

From the standpoint of therapy, sulfonamide compounds and artificial fever have been notable failures. In no case was the blood sterilized. In 1 instance of tricuspid and aortic involvement, ulceration through the intraventricular septum apparently occurred during treatment.

Abdominal Infections.—The presence of enterococci in great numbers in the feces suggests that these organisms should be intimately associated with many infectious processes originating in the peritoneal cavity and its associated organs. No direct published evidence is available which is pertinent, since specific differential tests have not been applied to the nonhemolytic streptococci frequently isolated from infections in and about the abdomen. It has been pointed out, however, that streptococci may be readily isolated from about 25 per cent of the purulent fluids obtained from patients with peritonitis following rupture of the appendix.[18]

During the present study enterococci were isolated from several intra-abdominal sources. On 5 occasions they were obtained from peritoneal exudates, twice in pure culture. Periarteritis nodosa, acute ulcerative enteritis and hemolytic jaundice were the predisposing diseases leading to peritonitis in 3 cases, and in 2 it followed operative rupture of the large bowel or bladder. No blood cultures were performed before or after death. All but 1 of the patients died. The one surviving was treated for seven days with sulfanilamide without its affecting the course of the disease. She finally recovered after drainage of an abscess in the cul-de-sac.

Nonhemolytic enterococci were isolated in association with colon bacilli (Escherichia coli) from the bile of 2 persons with acute cholecystitis and cholangitis. Both recovered after surgical intervention, with removal of stones in 1 and release of occlusive adhesions around the common duct in the other. The latter patient was twice explored surgically, and the bacterial flora of the bile was similar on the two occasions, one year apart.

16. Rantz, L. A.: Unpublished data.
17. Wallach, K.: Subacute Enterococcus Endocarditis, J. Mt. Sinai Hosp. **1**:80, 1934.
18. Altmeier, W. A.: The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis, Ann. Surg. **107**:517, 1938.

The pus obtained from 1 patient with an ischiorectal abscess contained many coagulase-positive staphylococci and hemolytic enterococci. Rapid healing occurred after surgical drainage and administration of sulfathiazole. The effect of chemotherapy could not be evaluated. On several occasions enterococci were isolated from operative wounds contaminated with fecal contents. Coliform bacilli were also present.

The nature of the infectious process leading to death in cases of acute peritonitis does not appear to be clearly defined. Observations made during this study are of interest in this respect. Cultures of blood from the heart have been made in 8 instances of abdominal infection following perforation of some part of the gastrointestinal tract. In 3 cases the blood was sterile; Proteus vulgaris was recovered in pure culture in 1, and enterococci were isolated in each of the others, twice in association with other organisms. In the 2 last-mentioned cases, culture of the peritoneal exudate revealed the same bacteria as were recovered from the heart's blood.

None of the patients from whom enterococci were obtained lived more than seventy-two hours after the onset of symptoms of peritonitis. No cultures of the blood were made during life, and none of the patients received therapy with a sulfonamide compound.

Enterococci are constantly present in the normal bowel and are therefore frequently recovered in cases of infections of the peritoneal cavity and associated organs, especially when a direct communication with the lumen of the intestine has been established. They are found, usually in association with other organisms, as the etiologic agents in many cases of acute peritonitis. It is of interest that cultures of blood from the heart in 8 instances of this disease revealed enterococci in 4. If it can be shown that the terminal events in fatal peritonitis are frequently associated with a generalized invasion of the body by enterococci, either alone or with other organisms, the rationale of either local or systemic treatment with sulfonamide compounds in such cases becomes less clear, since these organisms are exceedingly resistant to the action of these chemicals.

Antemortem and postmortem cultures of blood and of peritoneal exudate in cases of acute infections of the abdomen are of great importance for the purpose of establishing the nature and extent of the infectious processes in fatal and in nonfatal cases.

Infections of the Urinary Tract.—A recent study [19] of the urines of 650 patients in the medical wards of this clinic revealed that streptococci could be isolated from 14 per cent of them and that 27 per cent of these organisms were enterococci. A report by Porch [20] also indicates the frequency with which fecal streptococci may be recovered from this source.

A general impression is obtained from previous descriptions [21] of infections of the urinary passages that streptococci are usually responsible for mild disease of these organs, and this view is supported by observations previously made in this clinic.[19] It appeared at that time that the enterococci might cause a more severe infectious process than the other streptococci. The large number of articles

19. Rantz, L. A.: Urinary Tract Infections, in Steele, J. M., and others: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1942, vol. 1, p. 137.

20. Porch, M. L.: A Bacteriological Study of Streptococci Isolated from the Urinary Tract, J. Bact. **41**:485, 1941.

21. Culver, H.: The Importance of the Streptococcus in Genito-Urinary Diseases, J. A. M. A. **103**:635 (Sept. 1) 1934. Heckel, N. J.; Jensen, L. B., and Wood, I. H.: Streptococcal Infections of the Genito-Urinary System, Urol. & Cutan. Rev. **40**:564, 1936. Cabot, H.: Modern Urology, Philadelphia, Lea & Febiger, 1936, p. 513.

describing the extreme resistance of these organisms to sulfonamide compounds in vitro suggests that their eradication from infected urines is an important problem in urologic practice, but no adequate description of enterococcic infection of the urinary tract has been discovered.

Members of this group of streptococci have been isolated from the urines of 105 persons during this study. The data on 58 of these will now be considered in detail. The others have been eliminated, since their urines contained less than 500 bacteria per cubic centimeter. It was hoped that a more clearcut evaluation of the true importance of the fecal streptococci in infections of the urinary tract might be obtained by eliminating these examples of minimal or questionable infection.

Table 2 presents certain pertinent data in regard to these patients and the organisms isolated from their urines. It will be observed that approximately one third of the diseased persons were males; that the streptococci occurred in pure culture in 58.6 per cent of the cases and mixed with colon bacilli in 22.4 per cent and with staphylococci in 17.3 per cent, and that 27.6 per cent of these persons harbored hemolytic and 13.8 per cent proteolytic enterococci.

Insufficient difference in the type of disease caused by the fecal streptococci in infections of the male and of the female urinary tract exists to justify the description

TABLE 2.—*Cultural Observations on Enterococci Isolated from the Urine*

	Males		Females		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Total number	21	36.1	37	63.9	58	100
Enterococci isolated in pure culture	12	57.2	22	59.5	34	58.6
Staphylococci also present	5	23.8	5	13.5	10	17.3
Coliform bacilli also present	3	14.3	10	28.0	13	22.4
Hemolytic enterococci	8	38.1	8	21.6	16	27.6
Proteolytic enterococci	2	9.5	6	16.2	8	13.8

of the findings in the two sexes separately. The average age of 21 males from whose urines significant numbers of enterococci were isolated was 55; that of females was 39.

The Infectious Process: For the purpose of this study, infection of the urinary passages was considered to exist only if dysuria, frequency of urination during the day, pain in the flank or back and fever were present in some combination in association with the presence of abnormal numbers of pus cells in the urine. The application of these criteria to the group of patients under discussion reveals that in 6 males and 12 females, 31 per cent of the total group, no evidence of infection of the urinary tract could be demonstrated. Enterococci were isolated in pure culture from the urines of 17 of these patients.

Eight males and 10 females suffered from typical cystitis without evidence of renal involvement. In the urines of two thirds of these patients other organisms, usually coliform bacilli or staphylococci, were present in the urine in association with the enterococci.

Six males and 15 females presented signs, such as fever and pain in the flank, which indicated the presence of pyelonephritis. In only 5 of the 15 cases were enterococci the sole organisms isolated from the urine. A brief description of these examples of apparently definite invasion of the kidney by fecal streptococci is pertinent.

CASE 5.—A man of 65 was admitted to the hospital with a history of chills and fever for ten days. Sulfapyridine had been administered elsewhere, and total anuria developed after

he had taken 12 Gm. The results of physical examination on the patient's entry were not remarkable except for rales at the bases of the lungs and marked enlargement of the prostate. The renal pelves were lavaged for the purpose of dissolving the probable sulfapyridine calculi, and cultures of urine from this source showed many hemolytic enterococci. After this operation he began to void, but transient enterococcic bacteremia appeared. Many pus cells and organisms were present in the urine at all times. He recovered from the acute attack after a febrile illness of about three weeks without the use of chemotherapy, but the urine was never sterilized.

Case 6.—A 46 year old diabetic woman entered the hospital with acidosis, the carbon dioxide-combining power being 40 volumes per cent. Innumerable white cells were present in the urine on admission, but the temperature was normal. An acute febrile episode supervened on the fifth hospital day, at a time when her acidosis was well controlled. Pain in the flank was absent, but the urine contained many pus cells and 10 million hemolytic enterococci per cubic centimeter.

An inlying catheter was inserted, and she made an uneventful recovery after a febrile illness of three weeks' duration. Sulfanilamide was administered over a ten day interval in large doses but entirely failed to modify the course of the illness. Since that time she has had repeated episodes of infection of the urinary tract. Coliform bacilli were usually the etiologic agents, but enterococci also were always present.

Case 7.—A 75 year old woman entered the hospital suffering from daily chills and fever for three weeks in association with generalized abdominal pain. Physical examination revealed only moderate tenderness in both lateral aspects of the abdomen and a temperature of 104 F. (40 C.). The urine contained an immense number of pus cells and nonhemolytic enterococci. The leukocyte count was 22,000 per cubic millimeter.

Her temperature remained elevated for seven days and returned to normal by lysis. Sulfathiazole was administered for seven days after the temperature was normal, and during this time the urine became sterile. She made a complete and uneventful recovery.

Case 8.—A 17 year old girl was delivered of a normal child at term after a prolonged and difficult labor. An eight day febrile episode followed this and was associated with the appearance of huge numbers of pus cells and hemolytic enterococci in the urine. Uneventful recovery occurred and the urine returned to normal without special therapy.

Case 9.—A 59 year old woman whose left ureter was cut during an operation for resection of the rectum had a prolonged febrile postoperative course during which nonhemolytic enterococci and pus cells were present in the urine in large numbers. She eventually recovered, but sulfathiazole in adequate dosage failed to influence the course of the disease.

Factors Predisposing to Infection: All of the males and two thirds of the females in whom active infectious processes were present showed evidence of obstruction or mechanical manipulation of the urinary passages or suffered from another disease which predisposed to infection of these organs. Prostatic hypertrophy was demonstrated in 10 men, cord bladder in 2, inlying catheter in 1 and heart failure and diabetes each in 1. Eight of the infections in women followed postoperative catheterization; in 3 the infection was associated with severe cardiac failure, in 2 with renal stone in 2 with diabetes and in 3 with other serious generalized infections.

Results of Therapy: Twenty-seven of the group of patients with infections of the urinary tract under discussion received treatment with sulfonamide compounds. For 8 no culture was made before treatment was begun; 13 were found to have a mixed bacterial flora in the urine in association with enterococci, and 6 had the latter organisms present in pure culture. Nearly all of these 27 persons received from 4 to 6 Gm. of sulfathiazole or sulfadiazine a day for seven or more days. A few were treated with sulfanilamide. At the end of the period of chemotherapy enteroccoci could still be recovered from the urine, usually in immense numbers. In 1 instance the urine was sterile.

Other bacteria which had been present before treatment had, in every case, disappeared. It is of the greatest importance to point out that during the progress of chemotherapy in these cases all symptoms of infection of the urinary tract were

relieved and the urine became free of pus cells in nearly every instance, even though many enterococci could still be isolated.

Mandelic acid was administered to 3 of these persons and resulted in a prompt sterilization of the urine in 2.

Comment on Infections of the Urinary Tract: The previously recorded observations indicate that enterococci can be isolated in significant numbers from the urines of certain elderly men and middle-aged women. Very often no evidence of an infection of the urinary tract is demonstrable, and in such cases the enterococci are almost always present in pure culture.

In certain instances cystitis or pyelonephritis is present, and in most of these cases other organisms are recovered from the urine in association with the enterococci. In such cases if a sulfonamide compound is given the bacteria other than the streptococci usually disappear; the latter then remain in enormous numbers. In spite of this fact pus cells are absent from the urine and all symptoms have disappeared.

All of these observations indicate that the presence of enterococci in the urinary tract does not in most cases produce inflammation, symptoms usually being caused by the presence of associated staphylococci and coliform bacilli.

Treatment with a sulfonamide compound practically never causes sterilization of the urine when enterococci are present, but mandelic acid may do so. Since the presence of the streptococci does not always cause definite disease and since the urines of several of the patients already described became sterile spontaneously, there seems to be little indication for the specific therapy of enterococcic bacteriuria in the absence of signs of infection.

On a few occasions fecal streptococci were the cause of cystitis and pyelonephritis. In these instances the disease process was similar to that in which other organisms are the etiologic agents. A difference was the failure of some of these patients to respond to treatment with a sulfonamide compound with the usual prompt sterilization of the urine.

Mandelic acid should be valuable for the treatment of enterococcic cystitis. Because the limitation of fluids necessary to the administration of this drug is dangerous if pyelonephritis is present, only symptomatic therapy, including the ingestion of large volumes of fluid, should be undertaken in cases in which enterococcic infection of the kidney has occurred.

Miscellaneous Infections.—Nonhemolytic enterococci were isolated in pure culture from material obtained from the interior of the uterus in 2 cases of puerperal fever. One patient had a normal labor; the other, an incomplete abortion. One was treated with sulfanilamide; the other, with sulfathiazole. Both recovered uneventfully after febrile illnesses of three days' duration. Neither appeared to be seriously ill at any time. The etiologic role of the streptococci in these 2 instances of postpartum fever cannot be definitely determined, but it seems probable that they were responsible for the infectious process.

Cultures of material obtained from 3 ulcerative lesions of the skin, 1 syphilitic and the others traumatic in origin, revealed nonhemolytic enterococci and staphylococci. The streptococci are to be regarded as probable contaminants of no great significance.

Hemolytic enterococci and colon bacilli were recovered from pus aspirated from the right shoulder joint of an elderly man with colon bacillus bacteremia and aplastic anemia. At some time streptococci must have also been present in the blood, but they had disappeared when cultures were first made. He made a good recovery after surgical drainage of the affected joint without chemotherapy.

COMMENT

The enterococci form a group of hemolytic and nonhemolytic streptococci of special biologic and serologic properties whose normal habitat is the human bowel. They are exceedingly resistant to the bacteriostatic action of the sulfonamide compounds.

Recent observations have shown that these organisms are more frequently isolated from human clinical sources, other than the respiratory tract, than any variety of streptococci. The study described here was an evaluation of these organisms as a cause of infections in man.

It has been shown that fecal streptococci are infrequently responsible for disease of the respiratory tract, but 7 instances of otitis media have been observed in which these bacteria were etiologically involved. The disease is different from the usual streptococcic infections of the ear in that it occurs in infants and appears to have a shorter and milder course. A peculiar localized subacute meningitis associated with sepsis developed in 1 adult patient.

Enterococci are responsible for approximately 20 per cent of all cases of subacute streptococcic endocarditis. The clinical course of the infection in these cases resembles that caused by the more frequently isolated types of streptococci, but certain differences are apparent. The normal heart is more likely to be affected, and renal lesions are uncommon. Suppuration in the heart muscle and in organs peripheral to the heart probably occurs uniquely in enterococcic endocarditis. The administration of a sulfonamide compound does not sterilize the blood or affect the final outcome in these cases but may cause the temperature to return to normal for a brief period.

Enterococci, usually in association with coliform bacilli, are a common cause of peritonitis and other infections in and about the abdominal cavity. This is especially true if perforation of the gastrointestinal tract has occurred. The presence of fecal streptococci in the heart's blood post mortem in several instances of peritonitis indicates that sepsis due to these organisms may often occur. Their relationship to fatal outcome in cases of acute infections of the abdomen should be further studied.

Culture of the urine frequently reveals that enterococci are present in very large numbers. In many instances no evidence of infection can be discovered. When it is, other organisms are usually associated with the streptococci. Treatment with a sulfonamide compound results in elimination of bacteria other than the enterococci and disappearance of all signs of active disease. These observations demonstrate the very slight inflammatory properties of the enterococci in relation to the urinary passages. Occasionally this group of organisms does cause cystitis or pyelonephritis, and these infections are remarkable principally because of their failure to respond to sulfonamide compounds.

The results of this study indicate that the enterococci are bacteria of relatively low virulence and invasiveness but that they are not infrequently responsible for serious local or generalized infections. Hemolytic enterococci may be readily confused with the important members of group A if methods of identification are not precise. The nature of the infectious process and the response to therapy of disease caused by the two groups of organisms are not the same; so the importance of accurate differentiation between them is obvious.

Further clinical information of importance will probably be obtained as biologic and serologic study of the streptococci is widely applied and more examples of enterococcic infection are discovered and described.

SUMMARY AND CONCLUSIONS

The enterococci form a group of hemolytic and nonhemolytic streptococci of unique biologic properties and are members of the Lancefield group D.

Enterococci are exceedingly resistant to the bacteriostatic action of sulfonamide compounds.

Enterococci are more frequently isolated from human clinical sources, other than the respiratory tract, than any other streptococci.

Enterococci have been demonstrated to cause otitis media, endocarditis and infections of the abdomen and of the urinary tract.

The nature and course of these infections have been described.

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CONCENTRATION OF CARBON DIOXIDE IN EXPIRED AIR IN HEART DISEASE

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A disturbance in the respiratory function is the outstanding clinical feature of heart disease. Respiration and circulation serve a dual purpose in supplying oxygen to and removing carbon dioxide from the tissues. When the circulation fails, respiration is stimulated as a means of compensation. By measuring the extent of this stimulation, the degree of circulatory failure may be estimated. The ordinary methods of measuring respiration are unsatisfactory; the volume of air breathed must be measured in relation to the oxygen absorbed or the carbon dioxide produced. It has been shown that determination of the concentration of carbon dioxide in the expired air is a simple and highly accurate means of measuring respiration.[1] It is remarkably constant in large groups of subjects and shows little variation between the sexes or with wide differences in age.

Dyspnea is a common complaint in hyperthyroidism and in obesity, whether the heart is abnormal or not. Hyperthyroidism and obesity frequently occur in conjunction with heart disease and make the interpretation of dyspnea more difficult.

THE VOLUME OF RESPIRATION IN HYPERTHYROIDISM

In hyperthyroidism there is a greater demand for breathing. However, if the increase in the volume of respiration is proportionate to the increase in metabolism, the concentration of carbon dioxide in the expired air should remain constant. This study is based on 366 consecutively observed patients with hyperthyroidism. As with the group with normal metabolism, patients with known abnormality affecting respiration were excluded. In table 1 the group with hyperthyroidism is compared with the group with normal metabolism.

In hyperthyroidism the concentration of carbon dioxide in the expired air is relatively constant. With progressive elevation of the basal metabolism there is a slight but definite downward trend in the carbon dioxide pressure in both sexes: at its maximum in the very toxic group the difference is only about 3.5 per cent. This downward trend may result from some impairment in the efficiency of the circulation in tachycardia, from a mild acidosis or from the slightly higher average body temperature in hyperthyroidism. However, from the clinical standpoint, it is the striking constancy rather than the small variation which is most impressive. The course of a number of patients with severe hyperthyroidism has been followed through wide ranges of basal metabolism with only small fluctuations in the partial

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1. Boyer, P. K., and Bailey, C. V.: Concentration of Carbon Dioxide in Expired Air, Arch. Int. Med. **69**:773 (May) 1942.

pressure of carbon dioxide in the expired air. When hyperventilation does occur in persons with hyperthyroidism, it has essentially the same significance as in persons with normal basal metabolism.

THE VOLUME OF RESPIRATION IN OBESITY

For this study a series of 657 women aged 15 to 59 years was selected from the group with normal basal metabolism.[1] The subjects were chosen arbitrarily on the basis of the percentage of the actual weight in excess of the ideal weight calculated from standard height and weight tables. These subjects are grouped in relation to the normal female standard in table 2.

TABLE 1.—*The Influence of Hyperthyroidism on the Concentration of Carbon Dioxide in the Expired Air*

Basal Metabolism	Number of Subjects	CO_2 Tension of Expired Air: Mean Value, Mm. Hg	Standard Deviation	Coefficient of Variation	Probable Error of Mean
Females					
Normal range	1,613	20.01	1.38	6.93	±0.0023
+10 to +24	176	19.80	1.29	6.50	±0.066
+25 to +49	88	19.43	1.30	6.70	±0.094
+50 and over	24	19.28	1.31	6.80	±0.18
Males					
Normal range	408	20.31	1.45	7.13	±0.048
+10 to +24	34	19.91	1.64	8.24	±0.19
+25 and over	44	19.64	2.00	10.20	±0.20

TABLE 2.—*The Influence of Obesity on the Concentration of Carbon Dioxide in the Expired Air*

	Number of Subjects	CO_2 Tension of Expired Air: Mean Value, Mm. Hg	Standard Deviation	Coefficient of Variation	Probable Error of Mean
All females	1,613	20.01	1.38	6.93	±0.0023
Overweight 10 to 19%	198	20.07	1.39	6.94	±0.067
Overweight 20 to 39%	287	20.08	1.42	7.10	±0.060
Overweight 40 to 59%	122	20.16	1.35	6.70	±0.083
Overweight 60 to 79%	46	20.25	1.67	8.25	±0.166
Overweight 80 to 183%	54	20.84	1.53	7.35	±0.177

The breathing of these obese women so closely paralleled their metabolism that the concentration of carbon dioxide in the expired air remained nearly constant. In the extremely obese subjects, including a number of enormous persons, the partial pressure of carbon dioxide in the expired air was appreciably higher, which indicates a reduction in breathing proportionate to production of carbon dioxide. Through the remaining subgroups there appears to be a very slight tendency to underventilation as obesity progressed. We do not at present have an explanation to offer for this observation. It may be associated with the tendency to elevation of blood pressure in obese subjects. The actual weight of these subjects may in itself have tended to obstruct and depress respiration mechanically. Possibly the tendency to somnolence in obesity was a factor. However, as with variations in sex, age and basal metabolism, the constancy of the partial pressure of carbon dioxide in the expired air is the most striking feature.

THE VOLUME OF RESPIRATION IN HEART FAILURE

In patients with cardiac disease dyspnea has been attributed to an increase in ventilation in the presence of a reduction in vital capacity.[2] In 1897 Kraus [3] observed a decrease in the concentration of carbon dioxide in the expired air. Knipping and Moncrieff [4] and McMichael [5] demonstrated that normally ventilation is proportionate to the amount of oxygen consumed and to the amount of carbon dioxide produced and used these ratios as a means of measuring the increased ventilation in heart disease. The hyperpnea of heart disease can be measured accurately by the concentration of carbon dioxide in the expired air under basal conditions.

THE RELATION OF VENTILATION TO THE DEGREE OF CARDIAC FAILURE

For this study 138 patients with heart disease were examined under basal conditions. Most of these patients had been followed for some time in the cardiac disease clinic, and the diagnosis had been well established by the routine analysis of the history, physical examination and fluoroscopic, roentgenographic and electrocardiographic studies and any other laboratory procedures indicated. Other patients were selected from the hospital wards, where the same procedure was followed in establishing a diagnosis. The patients were classified according to functional capacity, depending on the clinical impression prior to the measurement of the volume of respiration. They were placed in the four classes recommended by the New York and the American Heart Association: [6]

Functional Classification of Patients with Cardiac Disease

Class I. Patients with cardiac disease and no limitation of physical activity.

Class II. (formerly IIA) Patients with cardiac disease and slight limitation of physical activity.

Class III. (formerly IIB) Patients with cardiac disease and marked limitation of physical activity.

Class IV. (formerly III) Patients with cardiac disease who are unable to carry on any physical activity without discomfort.

No attempt was made to select heart disease of any particular type, and the entire group includes a general cross section of patients with cardiac involvement; the etiologic and functional distribution is shown in table 3. The hypertensive group includes hypertensive patients both with and without demonstrable arteriosclerosis. The arteriosclerotic group all had essentially normal blood pressure.

In table 4 the average ventilation is expressed as the partial pressure of carbon dioxide in the expired air and also as the percentage of hyperventilation above the amount normally expected. A small number of class I cardiac patients had

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of Respiration: IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: Clinical Studies of the Respiration: V. The Basal Metabolism and the Minute Volume of the Respiration of Patients with Cardiac Disease, ibid. **20**:468 (Sept.) 1917. Harrison, T. R.; Turley, F. C.; Jones, E., and Calhoun, J. A.: Congestive Heart Failure: X. The Measurement of Ventilation as a Test of Cardiac Function, ibid. **48**:377 (Sept.) 1931.

3. Kraus, cited by Fishberg, A. M.: Heart Failure, Philadelphia, Lea & Febiger, 1937.

4. Knipping, H. W., and Moncrieff, A.: The Ventilation Equivalent for Oxygen, Quart. J. Med. **1**:17, 1932.

5. McMichael, J.: Hyperpnea in Heart Failure, Clin. Sc. **4**:19, 1939.

6. New York Heart Association, Criteria Committee: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Tuberculosis and Health Association, 1939, pp. 72-73.

concentrations of carbon dioxide in the expired air within the normal range. Of the 61 class II patients with cardiac disease, only 6 had carbon dioxide tensions at or above 20 mm. of mercury, while 17 had concentrations definitely below the range of normal. The average for the entire group shows a significant tendency to hyperventilation. It is interesting that this should be true of patients who are supposed to have only slight restriction in functional capacity. It is all the more impressive since these measurements were made under basal conditions when these patients had no feeling of dyspnea whatsoever. In this series none of the patients in class III or class IV had carbon dioxide pressures within the normal range. From group to group, as the cardiac functional capacity became progressively

TABLE 3.—*Distribution of Patients*

Etiologic Classification	Class II	Class III	Class IV
Congenital	2	2	..
Hypertensive	11	16	10
Rheumatic	33	10	11
Arteriosclerotic	15	16	5
Subacute bacterial endocarditis	..	1	..
Syphilitic	..	..	1
Hypertensive with renal complications	..	..	5
Total	61	45	32

TABLE 4.—*Ventilation in Patients with Cardiac Disease Grouped According to Functional Capacity*

	Number of Subjects	CO_2 Tension of Expired Air		
		Mean Value, Mm. Hg	Range, Mm. Hg	Average Hyperpnea
Normal	..	20.00	22.50-18.00	.....
Class II	61	18.56	21.47-16.31	7.8%
Class III	45	15.81	17.56-14.01	26.5%
Class IV	32	13.44	16.06- 9.04	48.7%

TABLE 5.—*Ventilation According to Etiologic Types in Comparable Degree of Failure*

Type of Heart Disease	Mean Tension of CO_2 in Expired Air *		
	Class II	Class III	Class IV
Hypertensive	19.15 (11)	16.06 (16)	14.26 (10)
Rheumatic	18.51 (33)	15.85 (10)	13.81 (11)
Arteriosclerotic	18.33 (15)	15.61 (16)	13.73 (5)

* Tension in millimeters of mercury; number of subjects in parentheses.

more impaired, the average amount of hyperventilation increased. In severely decompensated cardiac patients this excessive ventilation may be 100 per cent or more above that expected from the rate of carbon dioxide production. To this may be added the additional burden of an increased metabolism resulting from the labored respiration. The greatest degree of hyperventilation has been observed in cases of heart failure with an associated uremic acidosis.

THE RELATION OF VENTILATION TO THE ETIOLOGIC TYPE OF HEART DISEASE

In table 5 cardiac patients with comparable degrees of failure, as judged by the functional classification, are grouped according to the principal etiologic types. In general, all three types of heart disease appear to cause hyperventilation of

about an equal amount for comparable degrees of failure. It is interesting to note that the relation of types of disease within a functional class stands in the same order in all three groups, namely, hypertensive, rheumatic and arteriosclerotic. This sequence may arise from mere chance selection in this relatively small series; its consistency throughout all three classes suggests that it may be significant. It seems reasonable that such qualitative differences should exist between the types of heart disease. In all probability the blood flow through the brain is most effectively maintained with an elevation in systemic blood pressure and least effectively maintained when arteriosclerosis is present without hypertension, rheumatic heart disease falling between the two.

Pain rather than dyspnea is the criterion according to which anginal patients are usually classified. It might be expected that when at rest and without pain these patients would have normal cardiac function. Only a small group of patients

TABLE 6.—*Ventilation in the Anginal Syndrome*

	Mean Tension of CO_2 in the Expired Air *	
	Class II	Class III
All patients with cardiac disease	18.55 (61)	15.87 (42)
Patients with angina	18.47 (8)	15.62 (6)

* Tension in millimeters of mercury; number of subjects in parentheses.

TABLE 7.—*The Ventilation Response to Digitalization in the Principal Types of Heart Disease and of Rhythm*

Type of Disease	Number of Patients	Mean Tension of CO_2 in the Expired Air		
		Before Digitalis, Mm. Hg	After Digitalis, Mm. Hg	Percentage of Improvement
Rheumatic	5	13.52	17.23	27.5
Hypertensive	3	14.66	16.82	14.7
Arteriosclerotic	7	14.32	16.27	13.6
Type of Rhythm *				
Regular rhythm	5	13.04	15.33	17.5
Auricular fibrillation	9	14.73	17.29	17.4

* One patient, in whom conversion to regular rhythm occurred during digitalization, is not included.

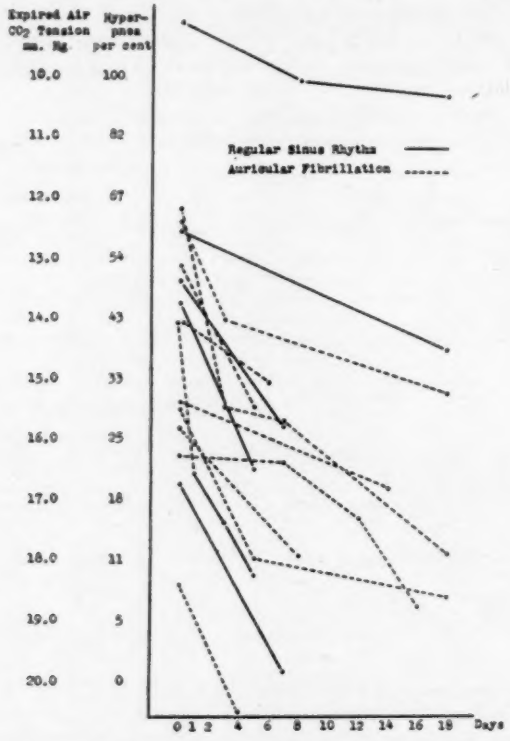
(14) with the anginal syndrome have been examined in our classified series. In table 6 these have been compared with other patients of the same functional class. It appears that even at rest without pain the anginal patient does not have normal cardiac function. Although these patients complain chiefly of pain, the prominence of this symptom may mask the dyspnea. Probably in all cases of arteriosclerotic heart disease both pain and dyspnea are present in relative degrees.

THE RESPONSE OF PATIENTS WITH CARDIAC DISEASE TO DIGITALIS THERAPY

Fifteen patients with varying degrees of cardiac failure were examined before treatment and one or more times during the course of digitalization. The results are shown in table 7 and in the chart. Ventilation was reduced in all cases. Improvement in the patients with rheumatic heart disease was more striking than in those with hypertension or arteriosclerosis; age is the probable factor. Improvement in patients with a regular rhythm is about the same as in those with auricular fibrillation.

THE INFLUENCE OF PAROXYSMAL AURICULAR FIBRILLATION ON VENTILATION

It is generally believed that auricular fibrillation with a rapid ventricular rate is in itself an inefficient rhythm. How much of the inefficiency is due to the rhythm and how much to an underlying organic heart disease is difficult to determine. Patients with hyperthyroidism and without severe organic heart disease are prone to temporary attacks of auricular fibrillation with a subsequent return to normal rhythm and normal cardiac function. In 5 cases of this type normal rhythm was reestablished without the use of digitalis. When the normal sinus mechanism pre-



The respiratory response to digitalization in 15 patients having varying degrees of cardiac failure.

vailed, the ventilation was normal; in all cases ventilation was increased during the periods of auricular fibrillation with fast ventricular rate. The average increase in the volume of respiration was 14.4 per cent.

THE RATE AND DEPTH OF RESPIRATION IN PATIENTS WITH CARDIAC DISEASE

In normal subjects both the respiratory rate and the volume of tidal air are subject to rather wide variation; the coefficient of variation of each is nearly four times that of the partial pressure of carbon dioxide in the expired air. Any statements made about the average respiratory rate and depth of breathing should

be interpreted with a knowledge of their variability. When respiration becomes unduly rapid and shallow, inefficiency results, not only from a relatively greater proportion of dead space but from an unequal and incomplete expansion of the lungs which tends to interfere with the gaseous exchange.[7]

In table 8 the rate and depth of breathing of the patients with cardiac disease listed in table 3 are compared with those of the 1,745 adult patients in the series with normal basal metabolism. From the cardiac disease group all patients with hyperthyroidism and uremia are excluded, because in both of these conditions the depth of breathing is increased. The average volume of tidal air is larger in males than in females at all ages; the normal value in table 8 is based on the proportion of males to females in each functional class.

As cardiac failure progresses, the increase in ventilation is largely accomplished by an increase in respiratory rate. This is in contradistinction to most other types of increased ventilation, in which both the rate and the depth contribute. When compared with that of normal persons, the breathing of patients with cardiac disease is not unduly shallow.

TABLE 8.—*The Rate and Depth of Breathing in Patients with Cardiac Disease*

	Number of Subjects	Respiratory Rate	Tidal Air, Cc. per Sq. M.	Normal Tidal Air, Cc. per Sq. M.
Normal adult subjects	1,745	15.6 ♀-14.4 ♂	219 ♀-255 ♂	
Cardiac patients, class II	44	17.2	222	229
Cardiac patients, class III	25	19.5	238	239
Cardiac patients, class IV	20	25.8	224	239

Hyperventilation in a person at rest is observed rarely in routine medical practice, and when it is found the usual cause is circulatory failure. Aside from cardiac disease one must consider the possible presence of acidosis, shock, certain types of severe pulmonary disease, severe anemia, hysteria and pregnancy.[8]

SUMMARY

In man, regardless of age, sex, basal metabolism or state of nutrition, the concentration of carbon dioxide in the expired air is strikingly constant.

Measurement of the concentration of carbon dioxide in the expired air during the determination of basal metabolism by the open circuit method is a valuable clinical aid in the study of the cardiac status and of the effectiveness of therapeutic measures; it is especially helpful in classifying patients with cardiac disease complicated by hyperthyroidism and obesity, in whom dyspnea on exertion is difficult to interpret; it is unique among methods of estimating cardiac function in that it is performed with the patient at rest; it measures the extent to which respiration compensates for circulatory failure.

7. Haldane, J. S., and Priestley, J. G.: Respiration, New Haven, Conn., Yale University Press, 1935. Christie, R. V., and Meakins, J. C.: The Intrapleural Pressure in Congestive Heart Failure and Its Clinical Significance, J. Clin. Investigation **13**:323, 1934.

8. Plass, E. D., and Oberst, F. W.: Respiration and Pulmonary Ventilation in Normal Nonpregnant, Pregnant, and Puerperal Women, Am. J. Obst. & Gynec. **35**:441, 1938.

KINETICS OF RESPIRATION IN EXPERIMENTAL PULMONARY EMBOLISM

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Previous investigators clearly demonstrated that the invariable response to diffuse embolism of pulmonary arterioles and capillaries is primarily that of tachypnea,[1] while the response following diffuse embolism of the moderately sized pulmonary arteries is characterized by both tachypnea and dyspnea.[2] It was concluded [3] that the underlying mechanism of these respiratory changes was different in that the rapid respiratory rate subsequent to the larger emboli was due apparently to anoxemia while that following the smaller emboli was the result of pulmonary congestion and edema. The latter appeared to operate by reflex action on the respiratory center by stimulation of the vagal nerve endings in the lungs.[4]

During the investigation of the cardiovascular dynamics of and the mechanism of death from experimental pulmonary embolism [5] we had occasion to confirm the essential differences in the character of respiration which follows moderately sized and miliary embolism. During the course of these studies we also noted that obstruction of the main pulmonary artery or of its two major subdivisions is followed by changes in respiration grossly similar to those following moderately sized embolism. The basic factors mediating the respiratory response to such major emboli were not immediately apparent, since arterial anoxemia was not a consistent aftermath [6] and pulmonary congestion and edema, when present, were usually late phenomena.[6]

Experiments were therefore instituted to attempt to elucidate the underlying mechanism of the exaggerated breathing associated with major pulmonary embolism. At the same time, for control purposes, experiments patterned after those of Binger, Brow and Branch [3] were performed. Our initial observations when compared with the results of these earlier investigators, however, presented discrepancies sufficient to indicate the need of a more complete reinvestigation of the entire subject. In the course of the present study we also undertook an analysis of the respiratory effects of papaverine hydrochloride, atropine, theophylline with ethylenediamine, metrazol and paredrine hydrobromide, as well as 95 per cent oxygen, to establish which, if any, of these pharmacologic agents might have therapeutic benefits.

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1. (*a*) Dunn, J. S.: Quart. J. Med. **13**:129, 1920. (*b*) Binger, C. A. L.; Brow, G. R. and Branch, A.: J. Clin. Investigation **1**:155, 1924.
2. Binger, C. A. L.; Brow, G. R., and Branch, A.: J. Clin. Investigation **1**:127, 1924.
3. Binger, Brow and Branch (footnotes 1 *b* and 2).
4. Moore, R. L., and Binger, C. A. L.: J. Exper. Med. **45**:655, 1927.
5. Megibow, R. S.; Katz, L. N., and Steinitz, F. S.: Surgery **11**:19, 1942.
6. Mendlowitz, M.: J. Thoracic Surg. **8**:204, 1938.

METHODS

Major embolism was produced by the method developed in this laboratory [6] in 24 dogs. Pea or radish seeds were employed to obstruct the moderately sized arteries in 13 dogs, and a 1:20 suspension of starch granules was utilized to induce arteriolar and capillary embolism in 16 dogs. The animals were anesthetized with soluble pentobarbital U. S. P. (sodium pentobarbital) intravenously (25 mg. per kilogram of body weight) except in a number of experiments of the major embolism type. In the latter the embolus was passed with the use of local procaine hydrochloride or temporary ether anesthesia. The rate and amplitude of respiration were recorded by a standard pneumograph. In 19 animals (11 with major, 4 with seed and 4 with starch embolism) the respiratory changes were correlated with the changes in pulmonary arterial pressure, which were determined directly from the main pulmonary artery (proximal to the obstruction) by means of the Hamilton needle manometer.[7] In the case of the unanesthetized animals the pulmonary arterial pressure was obtained by use of the London cannula technic developed in this laboratory.[8] The drugs to be used were injected intravenously and 95 per cent oxygen was administered, when desired, by placing the animals in a specially designed oxygen glass chamber and changing its gas content from that of normal atmosphere to as high as 95 volumes per cent of oxygen (O_2).[9] The oxygen and the carbon dioxide content of the blood were measured from samples of heparinized blood from the carotid artery, withdrawn under oil, prior to and following embolism (and after some of the therapeutic procedures) by the usual Van Slyke method. On several occasions the p_H of the serum was determined at the same time by the glass electrode method (Beckman p_H meter).[10]

RESULTS AND THEIR INTERPRETATION

1. The Changes Observed at Necropsy Following Major Pulmonary Embolism.—In order to interpret the respiratory changes following major embolism, it is essential to appreciate the alterations in the vascular system, heart and lungs demonstrable at necropsy. This interpretation is based on the autopsies of 24 animals with major embolism correlated with notes of the series reported previously from this laboratory.[11]

The effects of the major embolism on the heart were remarkably constant at necropsy regardless of whether the animal succumbed within a few minutes or after several hours. In all, the right side of the heart and the great veins appeared dilated, often to a marked degree. In contrast, the systemic veins were sometimes dilated and engorged and occasionally collapsed, depending on the degree of the pulmonary obstruction and the time of death (cf. previous report [5]). If death occurred early, the lungs appeared slightly emphysematous or, more frequently, pale and bloodless. If the animal survived for hours, however, focal areas of pulmonary congestion, edema and atelectasis were frequently discernible. The other viscera presented only varying degrees of passive hyperemia.

2. The Changes in Respiration Following Major Embolism and Their Cause.—Characteristically, after major embolism respiration quickened (chart 1) and became deepened and markedly labored. All accessory muscles of respiration were brought into action. Usually these alterations gradually became intensified. Terminally respiration usually slowed and appeared gasping and stertorous. The heart usually continued to beat for some time after respiration ceased. At some time during the course of most experiments cyanosis became apparent and was progressively intensified.

These changes in respiration were not dependent on a reduction in the oxygen content of the arterial blood or an increase in its carbon dioxide content in the

7. Hamilton, W. F.; Brewer, G., and Brotman, I.: Am. J. Physiol. **107**:427, 1934.
8. Katz, L. N., and Steinitz, F. S.: Am. J. Physiol. **128**:433, 1940.
9. Dr. D. Cohn, of the department of chemistry, designed this chamber and lent it to us.
10. Dr. I. Kaplan, of the department of chemistry, made these determinations of p_H.
11. Megibow, Katz and Steinitz.[5] Mendlowitz.[6]

five experiments in which blood gases were measured. Nor were the respiratory changes dependent on the development of an acidemia in the two experiments in which the p_H of the serum was measured. The development of anoxemia or its aggravation when present at the start of the experiment and the development of hypercapnia and acidemia when they occurred were much later and could have been responsible only in part for the increase in the respiratory difficulty. As a matter of fact, with the quickened respiration following the major embolus the arterial oxygen content and oxygen saturation increased slightly, the arterial carbon dioxide content fell slightly and the p_H of the serum became slightly more alkaline, as might be expected to follow an increase in ventilation. These changes in oxygen and carbon dioxide content can be seen in figure 1 by comparing the first with the second and the fifth set of readings. Apparently, then, the mechanism of the respiratory changes does not reside primarily in the development of anoxemia, hypercapnia or acidemia. This is further indicated, as far as anoxemia is con-

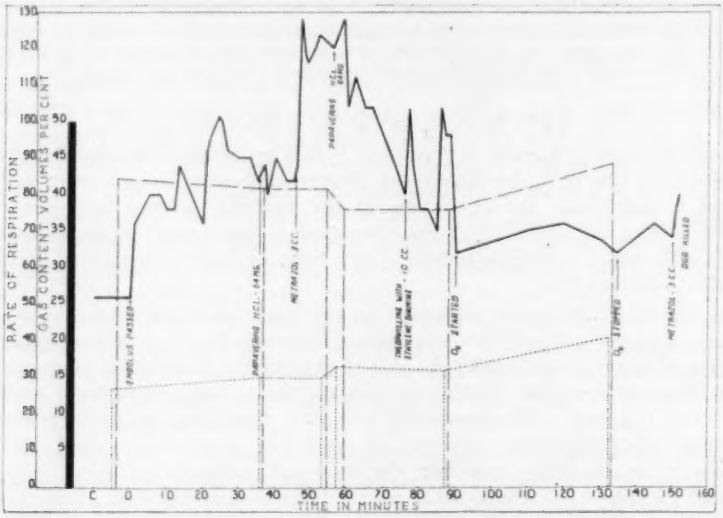

Chart 1.—Data obtained in a typical experiment with a major pulmonary embolus. The solid line indicates the rate of respiration, and the dotted line shows the oxygen (O_2) content and the dot-dash line the carbon dioxide content of arterial blood.

cerned, by the experiments with 95 per cent oxygen, in which it was found that, while oxygen therapy relieved the cyanosis and arterial anoxemia when present, it had little influence on the respiratory activity (fig. 1).

The fact that pulmonary congestion, edema and atelectasis occur only after a matter of hours, as evidenced in our series of autopsies, while the respiratory changes come on almost at once after embolization indicates that they too are not the primary mechanism for the tachypnea and dyspnea. This is substantiated by the occurrence of these respiratory changes in animals which succumbed too soon to show pulmonary congestion, edema and atelectasis at necropsy. In time, however, if the animal survives, decreases in vital capacity and elasticity of the lungs dependent on pulmonary congestion, edema and atelectasis contribute to augment the already increased respiratory rate and, together with arterial anoxemia, hypercapnia and acidemia, may be in large part responsible for the progression of the respiratory changes in fatal cases.

In our previous experiments [5] we demonstrated an abrupt elevation in pulmonary arterial pressure above the site of obstruction following major embolism. In eleven experiments of the present series the time relation of the respiratory changes and the changes in pulmonary arterial pressure was analyzed. In five of these experiments the respiratory changes occurred abruptly, almost at once, after the embolization. In these instances it was found that the tachypnea and dyspnea appeared coincidentally with the pulmonary hypertension.

In six of these experiments, however, no changes in rate or depth of respiration were detectable for periods varying from three to eighteen hours after embolism. In these the rise in pulmonary arterial pressure was slight or absent at first and developed only gradually over the next few hours at an accelerating rate, reaching levels of the order found in the experiments with immediate pulmonary hypertension about the time tachypnea and dyspnea developed. Apparently, then, the occurrence of these respiratory changes in major pulmonary embolism is dependent on a certain degree of pulmonary obstruction with a certain level of congestion and hypertension above the site of obstruction and/or a certain diminution in the flow of blood beyond the embolus. In these experiments with delayed effects, apparently the initial obstruction is of insufficient magnitude to lead to respiratory changes. Through the addition of antemortem thrombosis, however (which was demonstrable at necropsy), the obstruction finally reached the critical degree to cause sufficient congestion and hypertension above the obstruction and sufficient interference with flow below it to lead to tachypnea and dyspnea.

By accident it was found that that part of the congestion and hypertension confined to the pulmonary artery above the obstruction and the decrease in flow beyond the pulmonary embolus were not the essential factors. Thus in four experiments the passage of the embolus was followed at once by respiratory changes similar to those found in major pulmonary embolism, and the experiment was judged to be of this sort. Yet at necropsy in these 4 animals the embolus was found to have lodged near the mouth of the superior vena cava. In two other experiments tachypnea and dyspnea were found to occur following the passage of the embolus and the embolus was found at necropsy to have curled up in the right ventricle in such a way as to obstruct flow into this chamber. Experience with 1 dog, in which an embolus was found lodged in the inferior vena cava without obstructing the superior vena cava, demonstrated that interference with flow beyond the obstruction was not the cause of the respiratory changes. The obstruction to flow in this instance seemed as great as in the experiments on pulmonary embolism and embolism of the superior vena cava, and yet during this experiment tachypnea, dyspnea and other significant changes in respiration were absent.

It would appear, therefore, that the common element in the presence of an embolus in the main pulmonary artery or its major tributaries, in the right ventricle or in the superior vena cava at its mouth is congestion in the vascular bed drained by the superior vena cava and its tributaries.

This was tested directly in 3 anesthetized dogs. A metal cannula, 3 mm. in diameter, with a small balloon fastened at the end was passed down the right jugular vein to the junction of the superior vena cava and the right auricle under fluoroscopic control. On inflation of the balloon so as to obstruct the flow and stretch this region of the vena cava, an immediate increase in rate, depth and effort of respiration appeared, resembling that noted with major pulmonary embolism. This disappeared when the obstruction was removed by deflating the balloon, and the appearance and disappearance of these changes could be caused again and again.

The first possibility that suggested itself was that the respiratory changes were due to stagnation of blood in and slowing of blood flow to the respiratory center, leading directly to alterations in its rhythmic activity. If the tachynea and dyspnea were due to such a central origin, bilateral vagal section should have no effect on the pattern of respiration or, at least, not restore it to the pattern existing before embolization. In four experiments, therefore, bilateral vagotomy was carried out after embolization had led to the characteristic respiratory changes. In all, vagotomy led at once to a restoration of breathing to a rate below the control level; the breathing resembled that observed in animals without emboli following vagotomy. Apparently the central mechanism for the change in respiratory pattern after major pulmonary embolization is excluded, and a reflex origin involving afferent vagal pathways is indicated.

By exclusion, then, the mechanism appears to be reflex in origin, the reflex arising in the congested vessels above the obstruction, namely, in the superior vena cava and its major tributaries. Further, this reflex would appear to be a stretch reflex. Positive evidence in favor of this view was obtained in three experiments, in which the umbrella-ribbed cannula constructed in this laboratory for another purpose [12] was used. This cannula, it has been shown, can distend the vessel at the site of the umbrella ribs when they are extended without obstructing blood flow. Under fluoroscopic control, distention of the junction of the superior vena cava with the right auricle was found in these anesthetized dogs to cause augmentation in the rate, depth and effort of respiration, which disappeared when the distention was relieved. These phenomena could be repeated. Apparently by stretch a reflex was set up in this region, presumably in the end organs found by Nonindez,[13] which resemble those of the carotid sinus.

While stimulation of the root of the superior vena cava has been shown to be involved in this reflex stimulation of respiration, the possibility is not excluded that other regions of the superior vena cava and its tributaries, of the right auricle and right ventricle and of the pulmonary artery above the major embolus may also be stimulated by the distention and contribute to the reflex respiratory stimulation. End organs are known to be present in some of these regions, especially at the root of the pulmonary artery.

The interpretation that the changes in respiration in major pulmonary embolism are primarily reflex in origin, set up by stimulation of end organs in the root of the superior vena cava and perhaps elsewhere behind the embolus as a result of distention, accounts for all the facts observed in this study. It is, however, likely that subsequently other factors which may develop, such as anoxemia, hypercapnia, acidemia and decreases in the vital capacity and distensibility of the lungs, may contribute to maintain and aggravate the respiratory difficulties. The pulmonary changes may operate by contributing to the changes in gas content and p_H of the blood or by reflex action arising in the lungs themselves. In much the same way, slowing of blood flow to the respiratory center and stasis in this area may also be contributory, but these are all secondary to the primary reflex stimulation of respiration due to the congestion behind the obstruction, at least in the region of the root of the superior vena cava.

These results with major pulmonary embolism and embolism of the superior vena cava indicate that obstruction and distention not only are significant with embolism but may apply to any variety of distention of the right side of the heart, such as occurs in heart failure. The importance of such a reflex origin to respiratory

12. Ballin, I. R., and Katz, L. N.: Am. J. Physiol. **135**:202, 1941.
13. Nonindez, J. F.: Am. J. Anat. **61**:203, 1937.

stimulation in cardiac failure is thus clearly suggested. The dyspnea which occurs with failure of the right side of the heart, therefore, may be, at least in large part, reflex in origin because of distention of the root of the superior vena cava.

3. The Changes in Respiration Following Diffuse Moderately Sized Pulmonary Embolism and Their Cause.—Seed embolism of the pulmonary arteries which involves moderately sized arteries caused in all 13 animals quickened, deepened and stertorous respiration. While in 7 of the 9 dogs for which such correlations were made cyanosis and arterial anoxemia accompanied these respiratory changes (chart 2, first and second readings), in 2 the respiratory changes definitely preceded the anoxemia and cyanosis. Apparently arterial anoxemia is not necessary to cause the respiratory changes, although it plays a more important role than in the major embolism. In favor of this view is the fact that the inhalation of 95 per cent oxygen by the 2 dogs tested (chart 2), while relieving the arterial anoxemia and cyanosis, caused only a slight or moderate diminution in respiration and did not restore breathing to its preembolic control rate or depth. It is thus apparent that the respiratory changes cannot be explained entirely on the development of arterial anoxemia. This is contrary to the interpretation of Binger, Brow and Branch.[16]

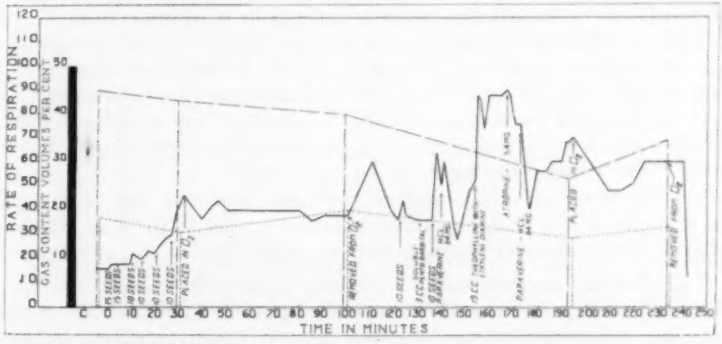

Chart 2.—Data obtained in a typical experiment with moderate-sized pulmonary emboli. The solid line indicates the rate of respiration and the dotted line shows the oxygen (O_2) content and the dot-dash line the carbon dioxide content of arterial blood.

Similarly, a correlation with the carbon dioxide content of arterial blood in these 9 animals showed no hypercapnia preceding or following soon after the onset of the respiratory augmentation. Thus the carbon dioxide content can be excluded as the etiologic factor. In like manner can pulmonary edema and congestion be excluded as the primary factors, since in 5 animals the characteristic changes in respiration were induced by the injection of large numbers of seeds, which led to a rapid death. At necropsy in such instances pulmonary congestion, edema and atelectasis were absent. Apparently reduction in volume or elasticity of the lungs is not per se responsible for the respiratory alterations, although its presence at necropsy in the animals succumbing after several hours indicates that it plays a later important contributing role.

The onset of the respiratory changes were found to coincide with the elevation in pulmonary arterial pressure in the 4 animals in which these two findings were correlated. Small amounts of seeds failed to cause respiratory changes or pulmonary hypertension. As more seed emboli were injected, greater respiratory changes followed and the pulmonary pressure rose. In the entire series of thirteen experiments, a rough proportionality between the number of seeds injected and the mag-

nitude of the respiratory changes could be established. The constancy of this correlation between pulmonary hypertension and respiratory stimulation suggests that in this form of embolism, as in major embolism, the mechanism for the respiratory changes resides in the vascular congestion behind the embolic obstruction. Thus, as in the major embolism, the mode of production of the respiratory alterations is presumably reflex in origin. In favor of this view is the fact that in two experiments section of both vagus nerves led to a marked slowing of respiration and the assumption of characteristic breathing seen in animals without embolization following bilateral vagotomy.

The possibility exists that in this form of embolism the respiratory changes are set up by irritation of end organs located in the pulmonary vessels by the seeds themselves acting as foreign body irritants. Against this view is the fact that the changes in breathing once established tend to intensify progressively, even though no further seeds are injected. This appears to be due to further obstruction of the pulmonary vessels by antemortem clot shown at necropsy to develop around the seeds and suggested by the gradual progressive rise in pulmonary arterial pressure.

All the findings in seed embolism of the pulmonary arteries, therefore, point to reflex respiratory stimulation which is consequent to distention of the vascular bed behind the embolic obstruction and is of a nature similar to that observed in major pulmonary embolism. A certain degree of distention is essential before this respiratory reflex is established, and its magnitude appears roughly proportional to the extent of the distention. This is not surprising in reflex action with a threshold in which more and more units are brought into play or the rate of discharge of those already operating can be increased.

In this form of embolism, however, arterial anoxemia and pulmonary congestion and edema play more significant subsidiary roles in the later stages in contributing to the respiratory changes than in major pulmonary embolism.

4. The Changes in Respiration Following Diffuse Pulmonary Arteriolar and Capillary Embolism and Their Cause.—Unlike major and moderate-sized embolism, diffuse minor embolism produced by starch resulted in tachypnea, unaccompanied by hyperpnea or dyspnea in our sixteen animal experiments. Like Binger and his associates [1b] we were unable to find any consistent correlation between the tachypnea and arterial anoxemia or hypercapnia. We made no correlation with p_H of the blood, but they reported also that no correlation could be made between the tachypnea and the p_H. In our series, however, arterial anoxemia developed early (chart 3, first and second samples, third and fourth samples) and seemed to play a significant part in the tachypnea. It is well known that shallow rapid breathing may be ineffective in ventilating the lungs, and, regardless of its cause, can by itself lead to anoxemia and hypercapnia, so that these changes may be the result of the tachypnea, the anoxemia tending to perpetuate the tachypnea. In 2 of these animals administration of 95 per cent oxygen relieved the anoxemia and cyanosis but had only a slight effect on respiration. Binger, Brow and Branch [1b] concluded from their studies that the tachypnea was the result of a reflex from the lungs carried to the respiratory center via the vagus nerves following the pulmonary congestion and edema which these emboli produce. The importance of this factor is supported by our experience, since pulmonary changes occurring after the starch embolization could be demonstrated much earlier than with the moderate-sized (seed) emboli, as our necropsy studies showed. The ability to slow the rate of breathing in 2 animals by bilateral vagotomy favors the view of a reflex mechanism of such pulmonary congestion but does not exclude the important mechanism of its causing anoxemia. Since the breathing in these animals, unlike that in the ani-

mals with other types of embolism, was not restored to the same level by vagotomy, some tachypnea persisted. However, it must be recalled that vagotomy operated in a similar manner in animals with the two other types of embolism in which the congestion was not primarily in the lungs. The possibility, therefore, exists in this form of embolism that congestion of the large pulmonary arteries, the right side of the heart and the superior vena cava may play an important role in causing the respiratory changes. At autopsy, the right side of the heart and large systemic veins in this form as in the other form show marked engorgement. Further, in 5 animals that had characteristic tachypnea postembolically, in which death occurred within two to five minutes following injection of large amounts of starch suspension, no evidence of pulmonary congestion or edema was seen grossly or histologically and only minimal histologic atelectasis was present. In these cases some other cause for the respiratory changes than a reflex from the lungs must therefore be sought.

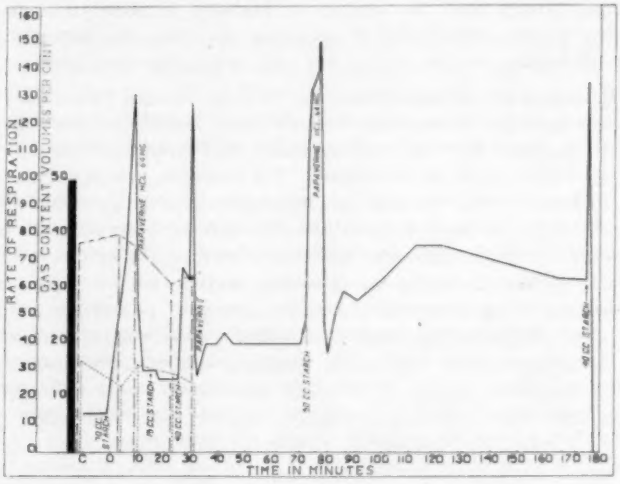

Chart 3.—Data obtained in a typical experiment with miliary pulmonary emboli. The solid line indicates the rate of respiration, and the dotted line shows the oxygen (O_2) content and the dot-dash line the carbon dioxide content of arterial blood.

Simultaneous recording of pulmonary arterial pressure and respiration in 4 dogs showed that in this type of embolism as in the others, respiratory changes appeared when pulmonary hypertension occurred. A certain minimal amount of starch suspension was required to cause both. Once tachypnea developed, it persisted and became intensified, and at the same time the pulmonary arterial pressure rose. The tachypnea here is thus again related to the obstruction, with its associated congestion behind the obstruction. It does not appear to be due to local irritation by the starch granules acting as foreign bodies, since if this were the case no aggravation of tachypnea with time should occur. This progression with time and the associated rise in pulmonary pressure appear to be due to the development of antemortem clots around the starch granules demonstrable at postmortem examination.

There is therefore no reason to doubt that a reflex mechanism exists with this form of embolism similar in nature to that associated with the major and

moderate-sized pulmonary embolism. But with this variety, unlike the others, it is moderated by some other mechanism. In part, the other mechanism is due to the anoxemia which develops early, and in part it may be a reflex from the congested lungs, as suggested by Binger, Brow and Branch.[1b] Neither of these two mechanisms, however, appears to explain all the findings. We therefore suggest the possibility that a reflex originates not in the lungs or the superior vena cava but in the smaller pulmonary arterial branches distended by the obstruction caused by the starch granules. This leads to the peculiar tachypneic respiration and overpowers the reflex arising in the superior vena cava and perhaps in the root of the pulmonary artery, which causes hyperpnea and dyspnea in other types of pulmonary embolism. These distended arteries may be so located as not to alter appreciably vital capacity or elasticity of the lungs, and in that sense our hypothesis differs from that of Binger, Brow and Branch.

Our results suggest, therefore, that end organs located in the vascular tree, in the root of the superior vena cava and probably elsewhere, as in the root of the pulmonary artery and the smaller pulmonary arteries, are susceptible to stretch, which initiates alterations in breathing patterns; the pattern of breathing produced is dependent on the site of the end organs so stimulated.

5. The Therapeutics of Rapid Breathing in Experimental Pulmonary Embolism.—In a discussion of the therapeutics of pulmonary embolism, obviously, the beneficial and deleterious effect of various drugs and procedures on all aspects of pulmonary embolism should be considered. For example, it is apparent that oxygen therapy is indicated whenever arterial anoxemia occurs, in order to obviate the deleterious effects of lack of oxygen. In this report, however, we shall confine ourselves solely to the possible demonstrable effects on the respiratory alterations.

It has already been noted in the preceding sections of this report that oxygen therapy, while relieving anoxemia when present with pulmonary embolism, was not equally effective in altering respiration with the different varieties of pulmonary embolism. Its effects were least with major pulmonary embolism and greatest with minute embolism; in the presence of moderately sized embolism its effect on breathing was intermediate between the first and the second type. It appears that oxygen therapy has its greatest benefit on respiratory effort in overcoming the rapid shallow type of breathing; this is important since it lessens the tendency for ineffective ventilation, which is part of this type of respiration.

Of the drugs tested only papaverine had a consistent and possible beneficial influence. Paredrine hydrobromide solution[14] (2 cc.), used 5 times, caused an increase in rate, depth and effort of breathing in animals with all types of pulmonary embolism and hence would exert a detrimental influence on respiration. Atropine sulfate (½ grain [0.03 Gm.]), used 13 times, theophylline with ethylenediamine (10 to 20 cc.), used 14 times, and metrazol (3 cc. of 10 per cent solution), used 6 times, exert a variable effect (charts 1 and 2). The inconstancy of the results with these drugs, which were not dependent on dosage or type of embolism, make them unreliable for relieving the dyskinetics of respiration.

Papaverine hydrochloride, 32 to 64 mg. given intravenously, was used 9 times with major, 7 times with moderate-sized and 15 times with minute pulmonary embolism. In all instances it caused a diminution in rate of respiration, after a variable preliminary acceleration. This was most marked in the animals with minute and moderate-sized pulmonary embolism and least marked in those with major embolism. The depth of breathing was increased with minute embolism and

14. Paredrine hydrobromide is p-hydroxy-α-methylphenylethylamine hydrobromide. It was used in an aqueous solution containing 20 mg. per cubic centimeter.

was decreased and made less difficult with moderate-sized and to an occasional minimal extent with major pulmonary embolism. The preliminary stimulation of respiration lasted ten to fifteen seconds, was at times pronounced and was similar to the effects of papaverine observed in anesthetized dogs without embolism. It is due to a direct stimulation of the respiratory center by the benzylisoquinoline alkaloids contained in this drug. The slowing and deepening of respiration which followed this preliminary effect appeared peculiar to the type of pulmonary embolism produced by minute emboli, with which there was a long-lasting effect, two to ten minutes or more (chart 3), during which the pattern of respiration was restored almost to normal. This effect could be maintained by administration of another dose of the drug when the effect of the preceding injection was dissipated. With moderate-sized pulmonary embolism this slowing effect was less marked, shorter in duration and associated with lessening of effort and depth of breathing. With major pulmonary embolism the slowing was still less pronounced and frequently entirely absent. When it occurred with major embolism, the depth and effort of respiration were lessened.

There can therefore be no doubt that papaverine exerts a useful role in restoring the kinetics of breathing to normal after pulmonary embolism, especially with the minute variety. It thus has a direct beneficial action in cases of pulmonary embolism, aside from its action in dilating the coronary vessels [15] and preventing the occurrence of ectopic ventricular beats, which might cause death by leading to ventricular fibrillation.[16]

Some evidence suggesting that papaverine operates directly on the pulmonary vascular bed was obtained in the following observations. In the 4 experiments with minute pulmonary embolism in which pulmonary arterial pressure was recorded simultaneously with respiration it was found that this drug caused at the time of respiratory slowing a decrease in pulmonary diastolic pressure despite the rise in systolic pressure, indicating a lessened resistance in the pulmonary bed. Visualization of the right ventricle, pulmonary conus and pulmonary bed in 2 other experiments on dogs with minute pulmonary embolism by means of injection of 70 per cent diodrast and roentgen examination showed a decrease in the size of the right side of the heart and pulmonary bed following the use of papaverine hydrochloride. These two types of observations suggest that this drug operates to reduce the resistance of the pulmonary arterial bed in pulmonary embolism, thereby relieving the congestion behind the obstruction and lessening the primary and subsidiary factors responsible for altered breathing. If this action were to dilate further the unobstructed peripheral pulmonary channels, especially if these are constricted—as assumed by many—it is apparent that its effect would be greater in peripheral types of embolism than in more central ones. For example, Landowne [17] in this department has demonstrated that when central arterial occlusion is present in the limb of man peripheral dilator procedures are less effective than normal in increasing flow.

These experiments with papaverine also support the view derived from other experiments presented in this report that the tachypnea occurring after minute embolization is primarily due to a reflex caused by distention of pulmonary arteries above the obstruction. Some support is lent also to the reflex origin of the respiratory changes in moderate-sized and major embolism.

15. Lindner, E., and Katz, L. N.: J. Pharmacol. & Exper. Therap. **72**:306, 1941.
16. Lindner, E., and Katz, L. N.: Am. J. Physiol. **133**:155, 1941. Elek, S., and Katz, L. N.: J. Pharmacol. & Exper. Therap. **74**:335, 1942.
17. Landowne, M.: Am. Heart J. **24**:50, 1942.

CONCLUSIONS

1. Respiration following embolism of major and moderately sized pulmonary arteries is characterized by tachypnea, dyspnea and hyperpnea; that following embolism of pulmonary arterioles and capillaries is characterized primarily by tachypnea.

2. These changes are not dependent on anoxemia, since the onset of rapid breathing is not infrequently associated with an increase in the oxygen content and per cent oxygen saturation of the arterial blood.

3. Alterations in carbon dioxide content and in p_H of the blood similarly play insignificant roles, since hypercapnia is inconstant and when occurring is transitory, while respiratory variations occur prior to any tendency to acidemia.

4. Actual decreases in volume and variations in elasticity in the lungs, such as follow congestion, edema and atelectasis, while later adding definitive increases to the already accelerated respiration, are by themselves not fundamentally implicated.

5. Evidence is presented to show that the respiratory changes are not mediated centrally by circulatory slowing through the respiratory center.

6. The fact that bilateral vagotomy constantly converts rapid postembolic breathing into slow vagal breathing is utilized as further evidence that the production of rapid breathing is peripheral rather than central.

7. The intimate relation of vascular obstruction to rapid breathing is indicated, and the fundamental mechanism with all varieties of pulmonary embolism is shown to be stimulation by distention of afferent nerve endings scattered throughout the pulmonary arterial bed, right side of the heart and superior vena cava.

8. Through rapid increases in elasticity of the lungs secondary reflexes are initiated, altering the primary respiratory response, and these account for the absence of dyspnea and hyperpnea in miliary embolism.

9. A brief consideration of the therapeutics of postembolic respiration shows that of the drugs studied, only papaverine exerts any beneficial action.

10. There is a possibility that reflexes of similar origin may be responsible for dyspnea in congestive heart failure and acute failure of the left side of the heart.

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ELECTROCARDIOGRAPHIC CHANGES WITH EXERCISE

THEIR RELATION TO AGE AND OTHER FACTORS

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The sensitiveness of the electrocardiograph to various stimuli and the consequent variation in tracings taken from the same person make it an important instrument in the study of myocardial function. Important also is the determination of normal variations under the stress of these stimuli.

Changes in the ventricular complexes during attacks of angina have long been recognized.[1] Similarly well known is the demonstration in latent coronary disease of characteristic electrocardiographic deviation after exercise. But [2] it has been pointed out also that inversion of the T wave may occur with such functional disorders as neurocirculatory asthenia and thyrotoxicosis.[3] It has been shown that excessive tobacco smoking can produce depression or inversion of the T wave.[4] Alkalosis and acidosis, the former produced by the simple procedure of hyperventilation with deep breathing, affect the amplitude of the T wave.[5] Anoxemia may flatten the T wave and depress the ST segment in normal persons.[6] Fear will produce changes in the T wave and ST segment similar to those of coronary disease,[7] and the mere taking of food may have its electrocardiographic response.[8]

A study by Tuttle and Korns [9] of electrocardiograms of 48 young male athletes taken before and after a season of training and competition showed changes in only 4 of the subjects. These changes mainly involved the T wave in lead III. One man had a diphasic T wave in lead II on the second tracing. Butterworth

1. (*a*) Missal, M. E.: Exercise Tests and the Electrocardiograph in the Study of Angina Pectoris, Ann. Int. Med. **11**:2018 (May) 1938. (*b*) Katz, L. N., and Landt, H.: Effect of Standardized Exercises on the Four-Lead Electrocardiogram, Am. J. M. Sc. **189**: 346 (March) 1935. (*c*) Vela, M.: Electrocardiographic Observations on Four Cases of Angina Pectoris During Attacks, Arch. cardiol. y hemat. **16**:1 (Jan.) 1935.

2. Duchosal, P. W., and Henny, G.: Modifications of the Electrocardiogram After the Exertion Test: Their Interest in Disorders of the Coronary Circulation, Helvet. med. acta **3**:652 (Oct.) 1936. Missal.[1a] Katz and Landt.[1b]

3. Graybiel, A., and White, P. D.: Inversion of the T Wave in Leads I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia, Am. Heart J. **10**:345 (Feb.) 1935.

4. Graybiel, A.; Starr, R. S., and White, P. D.: Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, Am. Heart J. **15**:89 (Jan.) 1938.

5. Barker, P. S.; Shrader, E. L., and Ronzoni, E.: Effects of Alkalosis and Acidosis upon the Human Electrocardiogram, Am. Heart J. **17**:169 (Feb.) 1939.

6. May, S. H.: Electrocardiographic Response to Gradually Induced Oxygen Deficiency, Am. Heart J. **17**:655 (June) 1939.

7. Mainzer, F., and Krause, M.: Changes of Electrocardiogram Brought About by Fear, Cardiologia **3**:286, 1939.

8. Gardberg, M., and Olsen, J.: Electrocardiographic Changes Induced by the Taking of Food, Am. Heart J. **17**:725 (June) 1939.

9. Tuttle, W. W., and Korns, H. M.: Electrocardiograph Observations on Athletes Before and After a Season of Physical Training, Am. Heart J. **21**:104 (Jan.) 1941.

and Poindexter,[10] interested chiefly in the question of the possible effect on the heart of blows on the chest, took electrocardiographic tracings of 35 boys and young men (aged from 16 to 24) before and immediately after boxing matches. They tabulated in detail minor changes in all the complexes, but in their conclusion they mentioned as worthy of note only the increase after exercise of the amplitude of the P wave in leads II and III and a decrease in the size of the T wave.

In our investigation we studied the immediate electrocardiographic response of normal persons to vigorous participation in various sports and correlated these findings with the factors of age, smoking and cardiovascular stability as measured by the Schneider index. As stated before, it would seem that tabulation of normal variations both in the resting state and after exercise might be of particular value.

METHOD OF STUDY

We picked at random 100 men from various groups that met regularly for exercise and recreation. The occupational and social status of the groups was diversified. The youngest subject was a 21 year old swimmer and the oldest a 67 year old volleyball player. For the purpose of statistical study the series was divided equally into those under 40 years and those over 40 years of age. The average age of the under-40 group was 30.7 years, as compared with 49.1 years for the over-40 group—a difference of nearly 20 years. Sports or activities participated in by the men examined were handball, squash racquets, volleyball,

TABLE 1.—*Averages of Subjects Studied, with Respect to Age, Smoking and Schneider Index*

Average age of subjects under 40	30.7 yr.
Average age of subjects over 40	49.1 yr.
Smokers	58%
Nonsmokers *	42%
Schneider index	
Over average *	66%
Under average *	34%

* The average Schneider index of the whole group was 14.85.

badminton, tennis, swimming, rowing, medicine ball, gymnasium apparatus work, bag punching and rope skipping, with the usual one-half to two hour workout.

The study in each case was as follows: The subject was seen immediately before he exercised and was questioned briefly in regard to known physical defects. Any one with cardiovascular disease was eliminated. Each subject was then given a Schneider index rating, which is obtained by a test of cardiovascular function and stability based on the reaction of blood pressure and pulse rate to change of position and exercise. This test will not reveal any organic cardiovascular disease unless there is secondary myocardial insufficiency, but it gives a fairly accurate indication of neurovascular fitness. The maximum score is 18, and any figure under 9 may be considered to be indicative of intrinsic myocardial damage. The next step in the examination was making an electrocardiogram with the subject in a recumbent position. He then took his exercise and returned immediately afterward for a second electrocardiogram. Because we wished to know what effect, if any, smoking might have on the Schneider index and on the electrocardiographic changes, notation was made as to whether the subject was a smoker or a nonsmoker. It is of interest that there was exactly the same percentage of smokers in both age groups, namely 58 per cent (table 1).

THE SCHNEIDER INDEX

Before we proceed with a discussion of the electrocardiographic findings a résumé of the Schneider index ratings makes an interesting corollary. As indicated in table 2, the average for the whole group was 14.85. In our tabulations, therefore, 15 was considered as above average and 14 as below. The difference of 1.5 between the two age groups, though definite, is inconsequential. The highest

10. Butterworth, J. S., and Poindexter, C. A.: An Electrocardiographic Study of the Effects of Boxing, Am. Heart J. **23**:59 (Jan.) 1942.

average score was made by the nonsmokers under 40 and the lowest by the smokers over 40. In fact, the use of tobacco was obviously almost as potent a factor in lowering the index as was age. In the group as a whole the ratio of those with an index above average to those with an index below average was 2 to 1.

THE ELECTROCARDIOGRAM BEFORE EXERCISE

In a study of the electrocardiograms of the aged (made with a group of supposedly healthy persons over 70 years of age) Levitt [11] found an increase in the QRS and PR intervals and concluded that this might be considered a normal finding in old age. As shown in table 3, our over-40 group had actually slightly shorter auriculoventricular and intraventricular conduction times than did the under-40 group.

TABLE 2.—*Schneider Index Averages as Affected by Age and Smoking* *

Group	Number of Subjects	Average Index
Whole series	100	14.85
Subjects under 40	50	15.6
Subjects over 40	50	14.1
Smokers under 40	29	15.2
Nonsmokers under 40	21	16.2
Smokers over 40	29	14.0
Nonsmokers over 40	21	14.3

* Possible maximum score, 18.

TABLE 3.—*Conduction Time Averages as Affected by Age and Exercise*

	Under 40	Over 40
Before exercise	(50 subjects)	(50 subjects)
PR_2	0.174	0.172
QRS_2	0.061	0.056
After exercise	(3 subjects)	(6 subjects)
PR_2	−0.02	−0.03
QRS_2	±0.02	±0.03

THE ELECTROCARDIOGRAM AFTER EXERCISE

Changes in conduction time with exercise were rare and insignificant and were found in both age groups. When such changes did occur, the PR interval in lead II was decreased, and the QRS interval in that lead was sometimes increased and sometimes decreased, but by such small amounts as to leave the intervals still well within normal limits.

Perhaps the most interesting and unexpected change after exercise was the alteration of the P wave in lead CF_4. This alteration was in most instances a frank inversion, and similar inversion was found only once in any other lead. It occurred in the electrocardiograms of 44 per cent of the whole group and, as shown in table 4, about twice as often in those of subjects under 40 as in those of men over 40. It occurred also more frequently in the electrocardiograms of smokers than in those of nonsmokers. Physical fitness as measured by the Schneider index was not a factor, however, since the change was shown as frequently by the over-average as by the under-average group. The possible significance of these figures is intriguingly uncertain.

11. Levitt, G.: The Electrocardiogram in the Aged, Am. Heart J. **18**:692 (Dec.) 1939

The susceptibility of the T wave to various stimuli has already been mentioned, and a study was therefore made of this phenomenon in the various groups. It occurred most frequently in leads III and CF_4 and consisted normally of changes in voltage, equally divided between increases and decreases. As shown in table 5, these changes in the T wave after exercise were found in 65 per cent of the whole group and more frequently in the under-40 than in the over-40 group. As with changes in the P wave in lead CF_4, the Schneider index was

TABLE 4.—*Changes in P Wave in Lead CF_4 After Exercise in Relation to Age, Smoking and Schneider Index*

Incidence: 44 per cent of whole group Group	Number in Group	Number of Subjects with Change in P_4	Per Cent of Group
Under 40	50	29	58
Over 40	50	15	30
Smokers	58	29	50
Nonsmokers	42	15	36
Index over average	66	30	45
Index under average	34	14	41

TABLE 5.—*Change in Voltage of T Wave After Exercise in Relation to Age and Smoking*

Incidence: 65 per cent of whole series Group	Number in Group	Number of Subjects with Change in T	Per Cent of Group
Under 40	50	36	72
Over 40	50	29	58
Smokers	58	44	76
Nonsmokers	42	21	50
Index over average	66	42	64
Index under average	34	23	68

TABLE 6.—*Change in Voltage of QRS Complex After Exercise* *

Incidence:		Percentage of Group
Under 40		78
Over 40		84
Voltage:	**Instances**	**Millivolts**
Increased	60	+0.3
Decreased	40	−0.4

* Changes in QRS occur in all leads but are greatest and most frequent in lead IV, and age is not a factor.

not a factor, but alterations in the T wave were found more frequently in smokers than in nonsmokers.

A change in the QRS excursion after exercise was the most common phenomenon of all. It was found in 81 per cent of all subjects and with the same frequency in both age groups. Increases were more frequent than decreases (3 to 2). The degree of change varied from 0.1 to 1.0 millivolt, the average increase being 0.3 millivolt and the average decrease 0.4 millivolt. Changes were most common and of greater degree in lead CF_4. These figures are recorded in table 6.

In the course of the study a few electrocardiographic curiosities were discovered which are worth reporting. In figure 1 is seen an inverted T wave in

lead CF_4 which becomes upright after exercise, and another flattened and distorted T wave in that lead which assumes a normal configuration after exercise. Both these tracings are from handball players in their early thirties who had maximum Schneider index ratings (18) and who were obviously free from any

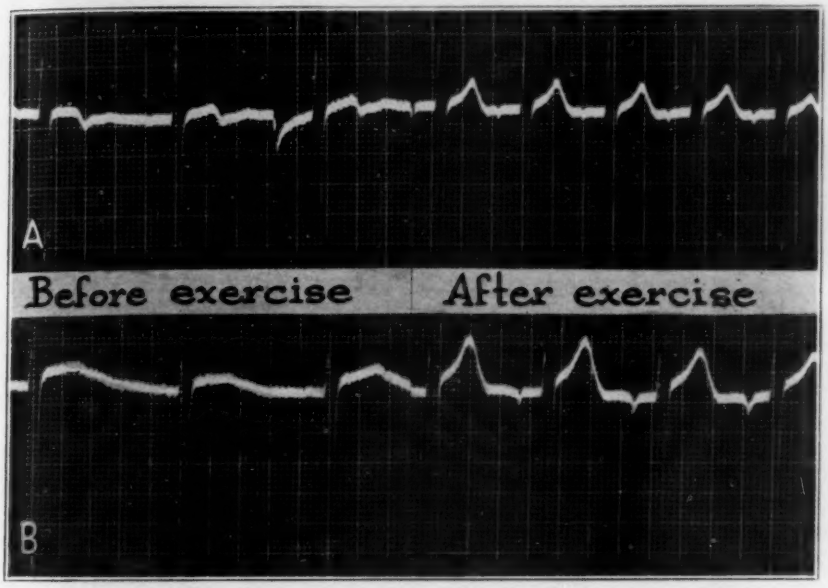

Fig. 1.—Lead IV: Changes in T wave. *A*, negative T wave becomes upright after exercise and P wave is inverted. *B*, change in contour of T wave after exercise; also inversion of P wave after exercise.

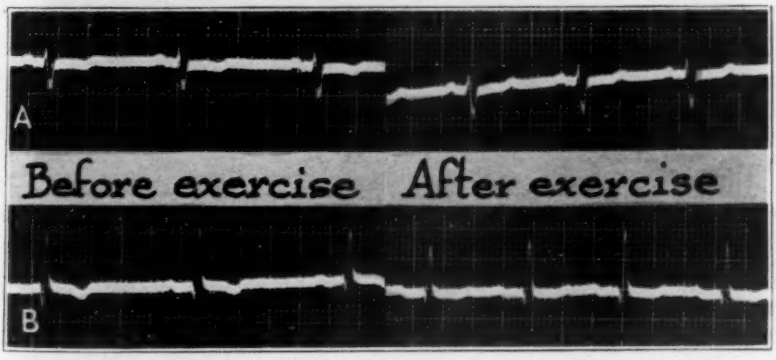

Fig. 2.—Lead III: Changes in T wave. *A*, negative T wave becomes positive after exercise. *B*, negative T wave becomes diphasic after exercise and QRS excursion becomes variable.

cardiovascular disease. In figure *2* are two examples of change of T_3 from negative to positive, or diphasic deflexion. A T_1 which changes from positive to diphasic is to be seen in figure 4 and in our series was a similar conversion of

T_2, the phenomenon thus being found in all leads. In figures 3 and 4 are seen distortions of the ST segment which might easily be called evidence of possible myocardial damage but which disappear after three hard games of handball.

As with the T wave, the QRS complex presented some unusual but clinically insignificant variations from the normal. Figure 5 shows a feathering of the QRS complex produced by exercise and also a similar distortion in another subject which was present before exercise and which disappeared after one and one-half hours of handball. In figure 2 is seen a series of QRS complexes which

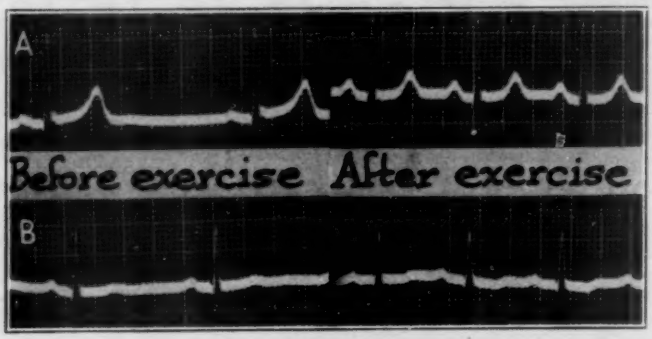

Fig. 3.—Leads I and II: Changes in ST segment and T wave. *A*, elevated take-off disappears after exercise in lead II and excursion of T wave decreases after exercise. *B*, T wave in lead I changes from positive to diphasic after exercise.

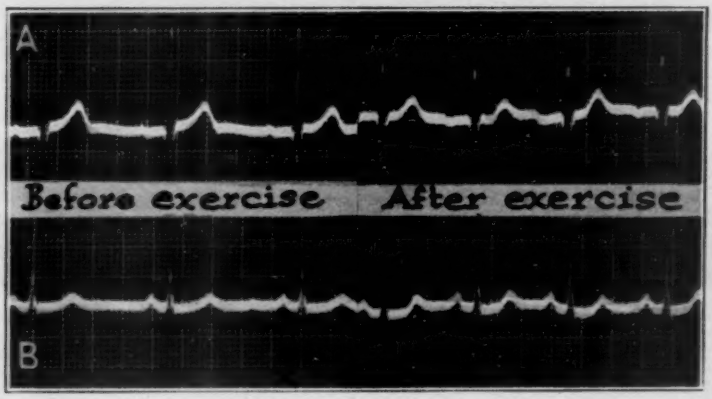

Fig. 4.—Leads III and CF_4: Changes in QRS complex. *A*, decrease of excursion of QRS complex in lead CF_4 and notching after exercise (note also inversion of P wave after exercise and monophasic QRS complex in lead CF_4 in normal man). *B*, splintering of QRS_3 disappears on exercise.

vary in voltage after exercise. In normal persons the QRS complex in lead CF_4 is presumed to be diphasic. Figure 4, however, shows a monophasic and notched QRS complex in that lead in a tracing from a 43 year old handball player with a Schneider index above average, and contrary to the accepted standard these peculiarities were found in several other obviously normal persons. Figure 6 shows a small distorted QRS_1 in a tracing from a 23 year old boxer with a

Schneider index of 18. These abnormalities, which might raise some suspicion as to the integrity of the myocardium, were found almost entirely in the under-40 group, in young adults with high Schneider index ratings.

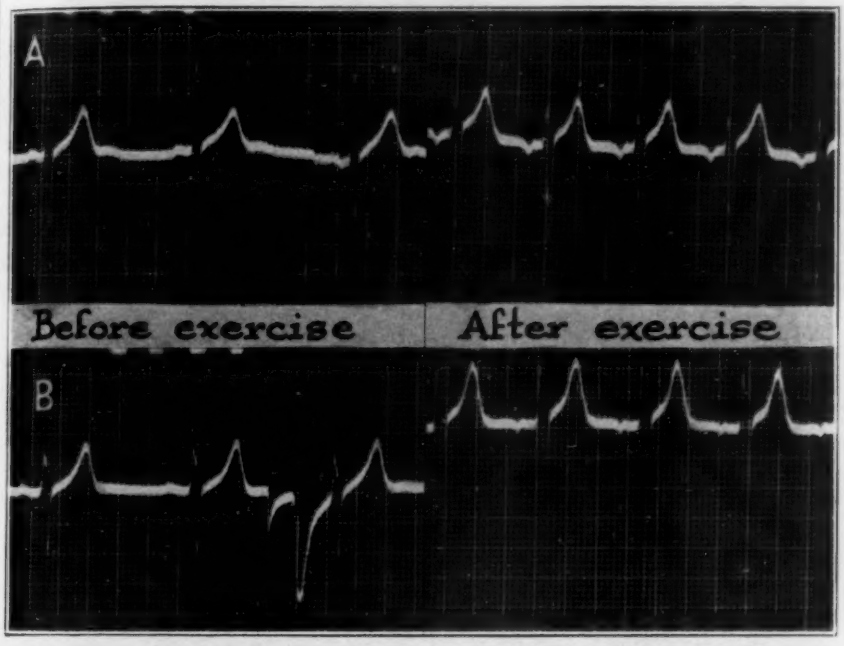

Fig. 5.—Lead IV: Changes in P wave and QRS complex. *A*, inversion of P wave and splintering of QRS complex after exercise. *B*, inversion of P wave and disappearance of notching of QRS after exercise. Twenty millimeter increase of QRS excursion after exercise.

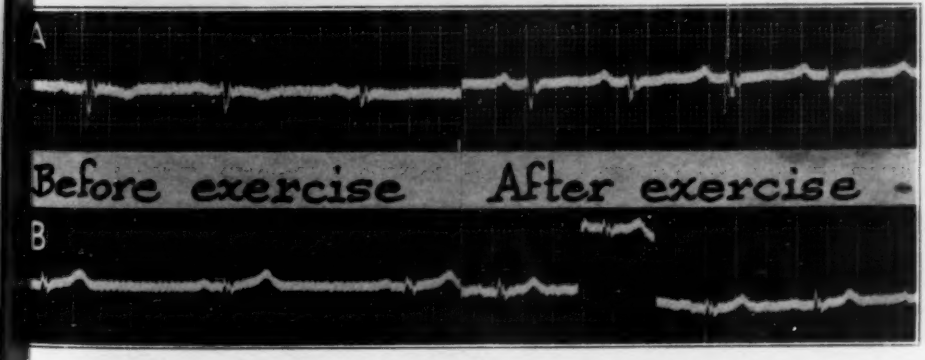

Fig. 6.—Leads I and III: Change in P wave and distortion of QRS complex. *A*, shows increase in voltage of P_3 after exercise and *B* distortion of QRS_1 in a normal young adult.

Distortion of the ST segment as the result of exercise has been reported as occurring in normal persons. In this study, however, distortion of ST or inversion of the T wave following exercise was found only in 3 persons, who had clinical

histories of cardiovascular disease, and who were not included in this series. We should therefore be suspicious of intrinsic myocardial damage when distortion of the ST segment or frank inversion of the T wave in significant leads is produced by exercise.

SUMMARY

With a series of 100 normal men a study was made of the electrocardiographic changes produced by vigorous participation in such active sports as handball and badminton. Tracings were taken immediately before and immediately after exercise.

There were no significant changes in the auriculoventricular or the intraventricular conduction time. Inversion of the P wave in lead CF_4 after exercise occurred in about half the group. Changes in the T wave were limited to changes in voltage. These were common, but no frank inversion of the T wave or distortion of the ST segment was found. A change in the size of the QRS complex was most common, being found in four fifths of the men in the series.

Half of the men studied were under 40 years of age, with an average age of 31, while the other half were over 40, with an average age of 49. There were no significant electrocardiographic differences between the two age groups, although the incidence of change when it did occur was greater in the younger group.

Concurrently a determination of the Schneider index was made for each subject. There was no marked difference in the average rating of the two age groups. There was no demonstrable correlation between the Schneider index rating and the electrocardiographic changes noted with exercise.

Three fifths of the men studied were smokers. The smokers had a Schneider index slightly lower than the nonsmokers, and changes in the P wave in lead CF_4 and in the T wave were more frequent in this group. In the course of the investigation there were found a few distortions of T, ST and QRS, which disappeared with vigorous and prolonged exercise and which may therefore be considered as occasional variants of the normal electrocardiogram.

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NIGHT CRAMPS AND QUININE

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A major task in geriatrics is management of manifestations of the degenerative changes peculiar to the aging process. Among these manifestations are two types of intermittent pain in the muscles of the lower extremities: the pain of intermittent claudication, and night cramps. The pathogenesis of intermittent claudication has come to be widely recognized; it is a pain of exercise, caused by inadequacy of blood supply in proportion to blood demand, much as is the anginal effort pain, and like the latter it is an expression of organic or spastic narrowing of vessels carrying blood to the muscles involved.

The pain of night cramps, like the pain of claudication, is intermittent, affects preponderantly the middle-aged and elderly and involves the same muscle groups. It is because of these obvious similarities that night cramps too have been generally considered a symptom of peripheral vascular disease. It is a common experience of specialists in vascular diseases to see patients with night cramps who have been referred for treatment of peripheral vascular insufficiency. This, almost uniformly, they do not have. What these patients all do show is some pathologic condition of the joints, nerves or ligaments of the lower extremities. The disorder may be a sciatic neuritis or a traumatic skeletal deformity, but the most frequent associated finding is chronic pathologic change in one or another of the weight-bearing joints.

The usual picture is that of a middle-aged man or woman who is free of muscle pain by day, whether resting or walking. He retires for the night without symptoms but is waked from sleep by an abrupt cramping pain in one or the other leg. On feeling the painful area he finds the muscles in hard contraction and tender. Vigorous rubbing of the calf muscles, hopping about or application of a hot towel causes gradual relaxation of the knotted muscle and relief from pain, but the area remains tender for a number of hours thereafter. The patient may return to sleep and be aroused repeatedly by recurring muscle cramps.

For a symptom so common and distressing, night cramps have attracted surprisingly little investigative attention. The incidence of night cramps in arthritic patients was studied by Pemberton,[1] who found that among patients with arthritis 32 per cent of the men and 43 per cent of the women had night cramps as a major complaint. A study by Pemberton and Foster [2] of the calcium-phosphorus metabolism in patients with arthritis long ago revealed that significant deviation from normal calcium balance does not occur in arthritis of either major type. My recent study [3] of calcium-phosphorus levels in sufferers from night cramps (of whatever cause) yielded uniformly normal values. The empiric administration to these patients of calcium salts in an effort to reverse a possible negative calcium balance proved of no value in alleviating the cramps.

Published with permission of the medical director, Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

1. Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1935, p. 53.

2. Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army Based on Four Hundred Cases, Arch. Int. Med. **25**:243 (March) 1920.

3. Unpublished data.

The basis for the present effective treatment of night cramps was provided by Kennedy and Wolf,[4] who in 1937 described the disappearance of muscle spasm in myotonia under the influence of quinine. Reasoning that a drug effective against one type of muscle spasm might well work against other kinds of spasm, Moss and Herrmann [5] in 1940 gave quinine to 15 patients with night cramps, with uniformly successful results. While noting that night cramps do not seem to be related to peripheral vascular disease, the authors did not attempt to explain why night cramps occur.

To understand the mechanism of the night cramp and the action of quinine in relieving it, it is useful to review the relationship of two muscular disorders, myasthenia gravis and myotonia, and two antagonistic drugs, prostigmine and quinine. In myasthenia gravis, the essential fault is diminished irritability at the myoneural junction,[6] that is, decreased sensitiveness of the motor end plate to the acetylcholine which is the chemical mediator of impulse transmission at the synapse. This fault is enhanced by the giving of quinine,[7] which (1) increases the refractory period of the muscle fibers and (2) by impairing irritability at the myoneural junction decreases still further the number of stimuli that can reach the muscle fibers. In cases of early, equivocal myasthenia, therefore, quinine has been diagnostically useful by quickening and making more evident the fatigability of the involved muscle groups.

As opposed to quinine, prostigmine promotes myoneural impulse transmission by destroying the enzyme choline esterase, which inactivates acetylcholine. In addition, it sensitizes the muscle fibers themselves to the action of acetylcholine. Hence the dramatic effectiveness of prostigmine in promptly abolishing the clinical manifestations of myasthenia gravis.

In myotonia the clinical manifestation is persistence of contraction in skeletal muscle after the end of voluntary stimulation. In abolishing this "after-contracture" or localized tetanus with quinine, Kennedy and Wolf [4] were making use of those properties of the drug just described: the ability of quinine to suppress repetitive muscle response by lengthening the refractory period and its curare-like depressing action at the myoneural junction.[8]

Night cramp in the lower extremity appears to be a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junctions by a stream of impulses from some neighboring source of irritation. This source of irritation may be arthritis in the hip or knee, weak feet or intrinsic inflammatory change in the nerves or muscles of the extremity. It is a fact frequently observed that as the irritative process in the skeletal structures subsides there is commensurate decrease in the frequency and severity of the muscle cramps. Conversely, aggravation of the irritative change, as by subjecting arthritic knees to long hours of weight bearing, is followed by noticeable intensification of the night cramps.

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4. Kennedy, F., and Wolf, A.: Experiments with Quinine and Prostigmin in Treatment of Myotonia Congenita, Arch. Neurol. & Psychiat. **37**:68 (Jan.) 1937.

5. Moss, H. K., and Herrmann, L. G.: Quinine for Relief of Night Cramps in the Extremities, J. A. M. A. **115**:1358 (Oct. 19) 1940.

6. Harvey, A. M.: Action of Quinine on Neuro-Muscular Transmission, Bull. Johns Hopkins Hosp. **66**:1 (Jan.) 1940.

7. Harvey, A. M.: Mechanism of Action of Quinine in Myotonia and Myasthenia, J. A. M. A. **112**:1562 (April 22) 1939.

8. While the explanation given in these paragraphs is an obvious oversimplification of the physiology of neuromuscular impulse transmission, omitting among other factors the vital role of migration of potassium between muscle tissue and serum and the related effects of rest and exercise in myasthenic and myotonic states, it does help to illuminate the parallel relationships involved in night cramps.

Essentially, the mechanism of cramp in the leg muscles is the same as that of rigidity of the abdominal wall in the presence of visceral inflammation. It represents a variety of the segmental visceromotor reflex, except that here the irritative focus in the spinal cord is produced not by visceral disease but by change in skeletal structures of the same segmental distribution as the muscles affected. Again, the effectiveness of quinine here is due in part to its action directly on muscle tissue; but more important is its effect in interrupting the reflex arc, by blocking myoneural impulse transmission. Quinine acts, then, much as does digitalis in depressing the bundle of His in auricular fibrillation, by cutting down the number of impulses that can get through to stimulate the muscle to contraction.

Besides the predisposing factor of neighboring foci of irritation, there is another factor which precipitates the attacks and is responsible for the occurrence of cramps during the night rather than by day. The patient frequently volunteers that he can bring on a cramp at will, merely by extending his lower extremity. He may go to sleep with a pillow folded under his knee to keep it flexed and so attempt to ward off an attack of cramps. This is effective until he changes position in his sleep, straightens his leg and is seized with a cramp. The reason for this phenomenon is the physiologic fact that the tension of muscle fibers increases as the muscle lengthens.[9] Beyond a certain degree of lengthening, muscle, like a rubber band, acquires the tendency to recoil into spasm. During the day, with the patient in the erect or the sitting posture, the calf muscles maintain a considerable degree of tone and are in a state of partial contraction against varying degrees of pull. In the recumbent posture, however, relaxation and lengthening occur. In muscles already abnormally stimulated by impulses radiating from an irritated segment of the spinal cord, extension of the extremity constitutes a trigger mechanism sufficient to throw the stretched muscle group into spasm. This is really nothing more than an exaggeration of the myotatic or stretch reflex which is made use of every time the ankle jerk is elicited by tapping the achilles tendon. The sharp contraction of the gastrocnemius and soleus muscles in response to the momentary lengthening of their fibers by the blow of the hammer is accentuated and protracted many times over in response to their being stretched abruptly by the sleeping patient.

Tables 1 to 4 summarize observations on 30 patients suffering with night cramps. Although the majority sought help primarily for associated disabilities, night cramps were a troublesome symptom in all the patients; in 9 the cramps were the chief complaint. The grievance all had in common was the impossibility of sleeping through the night undisturbed. Three patients had been unable for many months to sleep except in an armchair, because going to bed meant a succession of painful spasms in the muscles of the calf. One man refused to undergo a laparotomy, giving as a reason his fear of postoperative evisceration. He felt certain that each time he fell asleep he would presently find himself out of bed, as was his wont, rubbing his knotted calf muscles before he was conscious enough to control his actions.

The lesions constituting the irritative foci included arthritis, hypertrophic or atrophic, of the weight-bearing joints; sciatic neuritis, deficiency states with peripheral neuritis of glove-stocking distribution, weak feet and traumatic residua with skeletal deformities throwing unusual strains on one or more joints. A case of muscular spasm due to traumatic strain (not included in this study) was that of a patient with irritation of the temporomandibular joint which followed the use of a new denture. For two weeks after he had finally discarded the denture, the

9. Brown, D.: The Regulation of Energy Exchange in Contracting Muscles, Biol. Symposia **3**:161, 1941.

patient suffered agonizing trismus whenever he opened his mouth more than just enough to take a drinking tube. The masseter spasms disappeared after the first dose of quinine, and the patient was able to resume a soft diet without cramps.

TABLE 1.—*Etiologic Factors*

Patient	Age	Irritative Focus	Associated Conditions	Peripheral Vascular Status	Comment
P. K.	49	Atrophic arthritis, multiple joints	Secondary anemia	Normal	
I. B. D.	47	Atrophic arthritis, multiple joints	Bronchial asthma	Mild angiospasm	
H. J. C.	45	Traumatic deformity, left foot	Cholecystitis	Angiospasm	Fewer cramps when alkaline powders stopped
A. D.	45	Deficiency polyneuritis	Tabes dorsalis (no Charcot joints)	Normal	
L. T. W.	58	Weak feet	Leukemia	Normal	
H. C. S.	52	Arthritis, lower spine	Duodenal ulcer	Normal	No cramps 1 week after quinine stopped; given prostigmine ampules during roentgen series; cramps that night only
H. McM.	52	Weak feet	Hypertension; cardiac disease	Normal	
J. A. P.	44	Deficiency polyneuritis	Malnutrition	Normal	
R. S. V.	51	Sciatic neuritis	None	Angiospasm	
W. B. W.	48	Arthritic knee	Cancer, eye	Normal	
A. P.	57	Arthritic knees	Diabetes mellitus; obesity	Calcified peripheral vessels	
C. E. B.	48	Weak feet	Leukemia	Normal	
J. R.	58	Sciatic neuritis	None	Normal	
E. R.	50	Traumatic deformity	Malnutrition	Angiospasm	
J. F.	44	Deficiency polyneuritis	Coryza	Normal	
E. O. W.	54	Fibrositis, knees	None	Normal	
E. A. F.	52	Hypertrophic arthritis, multiple joints	Duodenal ulcer	Normal	
J. M.	60	Deficiency polyneuritis	Generalized arteriosclerosis	Angiospasm	
F. J. M.	44	Atrophic arthritis, multiple joints	Rheumatic cardiac disease	Angiospasm	
R. D. R.	52	Arthritis, lower spine	None	Normal	
F. M.	53	Arthritic knees, spine, etc.	Duodenal ulcer	Normal	Fewer cramps after alkaline powders discontinued
J. P. K.	55	Deficiency polyneuritis	Diabetes mellitus	Angiospasm	
H. P.	45	Sciatic neuritis	None	Normal	
P. F.	48	Weak feet	Recurrent appendicitis	Normal	
F. C.	51	Hypertrophic arthritis, multiple joints	Hypertension; cardiac disease; obesity	Angiospasm	
H. C.	63	Weak feet	Arteriosclerosis; cardiac disease	Normal	
O. T.	63	Deficiency polyneuritis	Pneumonia	Normal	
H. B.	52	Weak feet	Syphilis of the central nervous system	Normal	
V. V.	52	Hypertrophic arthritis, multiple joints	Hypertension; cardiac disease; prostatism	Calcified peripheral vessels	Prostigmine in course of roentgen studies caused recurrence of cramps, 1 night only
D. G.	38	Rheumatic arthritis, multiple joints	Rheumatic cardiac disease	Normal	

When, without the patient's knowledge, a capsule of acetylsalicylic acid was substituted on the fourth day, the trismus promptly reappeared and was again controlled with quinine.

In general, this was the pattern of response to quinine medication. In 28 of the 30 patients, including several who had not had a cramp-free night in months, administration of the first capsule of quinine at bedtime dramatically abolished the spasms. Trial of various quantities of the drug led to the adoption of 3 grains (0.19 Gm.) of quinine sulfate at bedtime as the optimal routine dose. For only 2 patients, 1 with severe sciatic neuritis, and 1 with traumatic deformity of the foot, were larger doses (5 grains [0.32 Gm.]) required to prevent the appearance of

TABLE 2.—*Relation of Predisposing Irritative Source to Site of Cramps*

Patient	Irritative Focus	Muscles Cramped
P. K.	Arthritic knees	Calf muscles, bilateral
I. B. D.	Arthritis of knees, ankles; ankylosis, right hip	Calf muscles, bilateral; right hamstrings
H. J. C.	Traumatic deformity, left foot	Calf and intrinsic foot muscles, right only
A. D.	Peripheral neuritis, bilateral	Calf muscles, bilateral
L. T. W.	Weak feet	Calf muscles, bilateral
H. C. S.	Arthritis, lower spine	Calf muscles, bilateral
H. McM.	Weak feet	Calf and foot muscles, bilateral
J. A. P.	Peripheral neuritis	Calf muscles, bilateral
R. S. V.	Sciatic neuritis, left	Calf and hamstring muscles, left only
W. B. W.	Arthritis of knees	Calf muscles, bilateral
A. P.	Arthritis of knees and ankles	Calf muscles, bilateral
C. E. B.	Weak feet	Calf muscles, bilateral
J. R.	Sciatic neuritis, right	Calf muscles, right only
E. R.	Traumatic deformity, left foot	Calf muscles, left only
J. F.	Peripheral neuritis	Calf muscles, bilateral
E. O. W.	Fibrositis of knees	Calf muscles, bilateral
E. A. F.	Arthritis of spine, knees, etc.	Calf muscles, bilateral
J. M.	Peripheral neuritis	Calf and foot muscles, bilateral
F. J. M.	Arthritis of spine, hips, knees	Calf and hamstring muscles, bilateral
R. D. R.	Arthritis of lower spine, hips	Calf muscles, bilateral
F. M.	Arthritis of spine, knees	Calf muscles, bilateral
J. P. K.	Peripheral neuritis	Calf muscles, bilateral
H. P.	Sciatic neuritis, left	Calf and hamstring muscles, left only
P. F.	Weak feet	Calf muscles, bilateral
F. C.	Arthritis of spine, hips, knees, ankles	Calf and hamstring muscles, bilateral
H. C.	Weak feet	Calf muscles, bilateral
C. T.	Peripheral neuritis	Calf muscles, bilateral
H. B.	Weak feet	Calf muscles, bilateral
V. V.	Arthritis of spine, hips, knees, ankles	Calf muscles, bilateral
D. G.	Arthritis of spine, knees, ankles	Calf muscles, bilateral

TABLE 3.—*Response to Initial Three-Grain Capsule of Quinine Sulfate at Bedtime*

Immediate abolition of cramps	28
Partial alleviation	2*
No response	0

* Complete disappearance of cramps when dose was raised to 5 grains.

TABLE 4.—*Effect of Discontinuing Use of Quinine After Three Days* **

Immediate recurrence (the following night)	6
Recurred within three days	10
Recurred third to fifteenth day	5
No recurrence after a month or longer	3

* Six patients left observation too soon to determine duration of relief.

cramps, and then only temporarily. Even these 2 reported definite alleviation in the severity of the cramps after the initial 3 grain (0.19 Gm.) dose.

A curious circumstance was that in several instances discontinuance of the use of the quinine capsule after three days was not followed by reappearance of the cramps, the patient remaining free of them a week or more and sometimes indefinitely. As is well known, the effects of quinine and related derivatives are evanescent, most of the drug being excreted in the urine within thirty-six hours of ingestion. In controlling auricular fibrillation with quinidine, it is a common experience that a nightly dose may be necessary to prevent reappearance of the arrhythmia at breakfast time. In view of this, the prolonged relief from cramps

after discontinuance of quinine cannot be attributed to cumulative action of the drug. Rather, the tendency to cramps must be thought to have decreased below threshold level, on account of the rest and treatment accorded in the meantime to the predisposing irritative lesion.

The sex and age of the patients included in this study were predetermined by their being chosen from among veterans of World War I. From experience elsewhere, however, it is clear that the preponderant majority of sufferers from night cramps are persons in the fifth, sixth and seventh decades of life; the average age of a group culled from general practice closely approximates the average found here. As for sex distribution, the impressive frequency among women of postmenopausal obesity and articular changes more than offsets the greater incidence of traumatic arthritis and secondary sciatic neuritis in men. The present series, then, is not to be taken as an indication of a greater incidence of night cramps among men.

The commonest single disorder predisposing to cramps in this group was arthritic change in the weight-bearing joints. There was no constant association of cramp in a particular muscle group with a corresponding site or type of arthritis. In a number of patients with cramps of the calf muscles the major pathologic condition was in the lumbosacral portion of the spine, rather than in the more distal joints. In the patients with weak feet, cramps in the calf muscles alternated on occasion with cramps in the intrinsic foot muscles. There was greater correspondence between irritative lesion and site of cramps in the patients with sciatic neuritis. In these the cramps were without exception restricted to the side of the inflamed nerve and involved usually the hamstring muscles as well as the calf muscles.

In none of the 30 patients did we find peripheral arterial disease of any importance. Moderate sclerosis of peripheral vessels was, as would be expected in persons of this age group, fairly common. In 2 men, an incidental observation in the roentgenograms of the joints was calcification of the coats of the popliteal and posterior tibial arteries. Eight patients had moderate peripheral angiospasm, manifested by some coldness of the feet and slight rubrocyanosis on dependency; in these men, too, however, the peripheral arteries were palpably pulsating and cutaneous nutrition was normal. Of the patients with angiospasm, all had normal vascular reserve; that is, they responded to a thermal stimulus with a normal degree of cutaneous vasodilation in the lower extremities.

COMMENT

An interesting consideration is the relationship of night cramps in the middle-aged and elderly to muscle cramps associated with other clinical disorders. In pregnancy, for instance, night cramps are a frequent complaint. Although the obvious mechanism which suggests itself is the tendency of the mother to have a negative calcium balance, the restriction of the cramps to the calf muscles and their occurrence in the last weeks of gestation point to the more likely hypothesis that pressure of the fetal head on the sacral nerves may be the source of irritation. Night cramps then develop in the same way as in the patients here described.

The therapeutic use of quinine in late pregnancy has been a matter of dispute among malariologists. There is good authority [10] for the belief that a 3 grain (0.19 Gm.) dose does not exert sufficient oxytocic effect, even on the gravid uterus, to endanger the pregnancy. The malaria inoculation treatment of dementia paralytica, with its concomitant use of quinine, is successfully administered to

10. Manson-Bahr, P. H.: Manson's Tropical Diseases, ed. 10, Baltimore, William Wood & Company, 1936, p. 71.

pregnant women. There are, besides, numerous instances on record of pregnant women treated with full antimalarial doses of quinine who did not abort.[11]

The tendency to muscle cramps in alkalosis was observed to play a part in 4 of the 30 patients. These men had been on a regimen for peptic ulcer and had been treating themselves with considerable quantities of alkaline powders. Before quinine was given, they were changed to a regimen which excluded alkaline medication. Three of the 4 observed an appreciable diminution in severity and frequency of the cramps. It would appear that in these men the disturbed acid-base balance had acted as a spasm-inducing factor in addition to the arthritis, by increasing further the irritability of the muscles.

The muscle cramps of athletes may be of the immediate type, a manifestation of the marked hyperpnea of effort, and of the increased muscular irritability associated with the consequent elevation in p_H.[12] Or they may be delayed and appear at night after a day of prolonged and strenuous exertion, particularly when previously little used muscles have been brought into play. Here an evident myositis has developed (stiffness and tenderness of the muscles for days following); the inflammatory changes in the muscle proper constitute the irritative focus and play the same role as the older patient's inflamed joint or nerve.

With injuries of long bones, the intense spasm of large muscle masses is probably more a matter of strong efferent stimulation from an irritated cord segment than a result of direct pressure of bone fragments. This muscular spasm, which often presents a considerable problem in the management of fractures, should on theoretic grounds be just as responsive to adequate quinine medication as similar types of spasm already have proved to be.

Tetanus and strychnine poisoning, of course, do their damage in the central nervous system primarily; still, their clinical effects are on the skeletal musculature. The difference between other types of muscle spasm and the spasms in these two conditions is a difference of degree rather than of kind. In tetanus and in strychnine poisoning the muscular activity is so widespread, so intense and so protracted that life processes, especially respiration, may be made impossible and the patient may die. These two irritative states have this in common with the other varieties of muscle spasm previously mentioned; the stimulation of the muscles to contraction and the maintenance of the contracted state depend on nerve impulses originating centrally and reaching the muscle fibers across the myoneural junctions.

Use of cinchona derivatives in man, by mouth and by vein, has already been tried extensively enough to demonstrate the safety and effectiveness of these drugs in controlling muscle spasm. A notable example is the recent successful prevention of fractures in the course of convulsive therapy with metrazol[13] through the use of a synthetic quinine preparation. There is therefore good reason to believe that the use of quinine as an antispasmodic drug may be extended to other generalized spastic states of the skeletal musculature. A priori, so powerful an antitetanic agent should be a decisive ally against strychnine poisoning and tetanus. With the former the problem is to keep the victim alive long enough to allow elimination of the poison. As for tetanus, the present accepted management depends on antitoxin and sedation. The effects of antitoxin are limited by the fact that

11. Yorke, W., and Murgatroyd, F.: Malaria, Ann. Trop. Med. & Parasitol. **25**:551, 1931.

12. Best, C. H., and Taylor, N. B.: Physiologic Basis of Medical Practice, Baltimore, William Wood & Company, 1937, p. 1101.

13. Bennett, A. E., and Cash, P. T.: Curarization with Quinine Methochloride to Prevent Traumatic Complications of Metrazol Shock Therapy, Psychiatric Quart. **15**:351 (April) 1941.

it cannot reach the toxin already combined with nerve tissue; it neutralizes only toxin elaborated at the wound and circulating in the blood. Heroic sedation, on the other hand, produces profound depression of the vital centers without accomplishing more than partial relaxation. It contributes materially to the incidence of a major cause of death in cases of tetanus, pulmonary complications.

What is badly needed with both conditions is the insulation for a number of days of the skeletal musculature against the ceaseless assault of stimuli from the central nervous system. The established pharmacologic capacity of quinine to interrupt the transmission of neuromuscular impulses, and its proved effect clinically against myotonia and night cramps suggest its probable value in the treatment of tetanus. In time of war, with tetanus inevitably on the increase, the use of a safe, well known and simply administered drug to hold in check the unremitting spasms is worthy of trial.

SUMMARY

A study of a group of 30 patients with night cramps is reported.

A theory of the mechanism of night cramps is offered and the effectiveness of quinine described.

Use of quinine to control muscular spasm in other clinical states, particularly tetanus and strychnine poisoning, is suggested.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW OF THE LITERATURE FOR 1942

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JAUNDICE FOLLOWING VACCINATION FOR YELLOW FEVER

The laboratories of the International Health Division of the Rockefeller Foundation have been active since 1936 in the development and production of a vaccine which by a single injection provides active immunity of long duration against yellow fever.[1] As a result of the war emergency the demand for this vaccine has been so great as to require its production on an unprecedented scale.

The distribution of yellow fever vaccine manufactured by the Rockefeller Foundation in New York in 1941 [2] was as follows:

	Doses	
United States Army	959,300	
United States Navy	960,000	
United States Public Health Service	3,000	
Panama Canal Zone	4,000	
Virgin Islands	12,000	
Total for United States Government		1,938,300
West Africa	152,000	
South Africa	158,000	
East Africa	1,662,380	
Total for Africa		1,972,380
India		222,000
Brazil		100,000
Singapore		28,000
Grand total		4,260,680

Great interest was aroused when it was reported by Army authorities in July that an epidemic of jaundice had developed among troops in the United States and abroad. This epidemic started in March and increased until a total of 28,585 cases was reported in July, when it was brought under control.[3]

Circular letter no. 95 from the Surgeon General's Office [4] reported that in this epidemic the clinical course of the disease had been remarkably uniform in the great majority of patients. The disease resembled most closely the so-called

From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Departments of Medicine and Surgery, New York Post-Gaduate Medical School and Hospital, Columbia Univestity.

1. Fox, J. P., and Cabral, A. S.: The Duration of Immunity Following Vaccination with the 17D Strain of Yellow Fever Virus, Am. J. Hyg. **37**:93 (Jan.) 1943.
2. Fosdick, R. B.: Report of the President of the Rockefeller Foundation for 1941-1942.
3. Jaundice Following Yellow Fever Vaccination, editorial, J. A. M. A. **119**:1110 (Aug. 1) 1942.
4. The Outbreak of Jaundice in the Army, Medicine and the War, J. A. M. A. **120**:51 (Sept. 5) 1942.

catarrhal jaundice or epidemic hepatitis of unknown cause. The onset was gradual, often imperceptible, until the appearance of jaundice. Increased susceptibility to fatigue, lassitude and anorexia were common prodromal or early symptoms, and in many cases, were the only symptoms. Nausea and vomiting occurred, and diarrhea sometimes preceded other symptoms. Fever was absent, or the temperature was but slightly elevated. The leukocyte count usually was normal; occasionally it showed a relative increase of monocytes. Pains in the joints and urticaria were present in about 20 per cent of cases. Dark-colored urine, yellow skin and scleras, and light-colored stools were usually noted. The liver was found to be enlarged and tender in about 20 per cent of cases. Bile pigments appeared in the urine and the blood. The icteric indexes ranged from 15 to 200, occasionally to 300. Prothrombin levels were reduced, and the excretion tests, such as the bromsulfalein test, indicated various degrees of disturbance of hepatic function. In most of the cases the disease was mild, and many cases were discovered only at special inspections. In a smaller but nevertheless considerable number the disease was more severe, with various stages of hepatic insufficiency being noted.

In general, recovery followed in four to eight weeks. In some stations convalescent camps were established to permit continuation of supervision of diet and activities in a regimen by which the patient was returned to duty gradually. Prognosis was favorable. Sufficient evidence is available to warrant the statement that recovery was complete in the vast majority of cases and that permanent damage of the liver occurred in only a few.

In the fatal cases of hepatitis observed during the year, death usually occurred from two to six weeks after the onset of the disease. The earlier stages of hepatitis were rarely observed by the pathologist. The chief pathologic lesions were those of an acute or subacute yellow or red atrophy of the liver. The earliest lesions consisted of frank necrosis of liver cells in the central parts of the lobules. Inclusion bodies were not present at any stage, the lesions thus differing distinctly from the lesions of yellow fever. Both the destructive process and the removal of debris by lysis were rapid. Within ten days the bulk of the necrotic material had usually been removed completely. The stroma was rarely damaged to any extent; in many areas the lobular framework remained intact. In most cases the destructive process was not diffuse, the severity of the damage tending to vary in different parts of the liver; in some areas the hepatic tissue was almost completely destroyed, whereas in others only the central parts of the lobules were necrotic. Unlike many forms of destructive hepatic diseases, this form did not have fatty changes as a conspicuous feature. Repair of the injured liver was brought about mainly by multiplication and hypertrophy of the remaining liver cells. The resulting lobules tended to be very large and were often of atypical construction. Destruction of liver tissue and removal of debris in this disease were invariably accompanied by inflammatory reaction, so that the term "hepatitis" is proper.

Changes in organs other than the liver were common. Of particular interest was the marked edema, often accompanied by intense inflammation, of the gastrointestinal tract. Although any part of the tract, including the esophagus, could be involved, the changes were usually most pronounced in the cecum. The relation of these lesions to the hepatitis was not determined. The kidneys presented the condition commonly known as biliary nephrosis (cholemic nephrosis). An acute or subacute splenic tumor usually was present. Hemorrhages, often extensive, in serous and mucous membranes were likewise common. The central nervous

system often showed changes similar to those found in it as a result of other severe toxic metabolic disturbances.

It must be emphasized that the extensive damage observed in the rare fatal cases was not duplicated in the nonfatal cases. It is more than probable that "yellow or red atrophy" represents the extreme end of a scale of lesions on which there are many gradations from the usual slight and readily reparable injury, such as occurs in the average patient, to the extensive destruction of tissue in the one who succumbs. In those who died from accident or disease subsequent to an attack of jaundice, little or no evidence of preceding hepatic damage was found. All information available indicated that in the average patient the damage done to the liver was slight and repair prompt and complete.

Etiologic investigations, started in March, seemed to offer a promise that the jaundice-producing agent might be discovered ultimately. The results at the time of the initial public report had been negative as far as the demonstration of a transmissible agent was concerned. These negative results, however, served to exclude a number of infectious diseases in which jaundice occurs. The outbreak of jaundice in the Army was not Weil's disease or any other type of leptospiral infection. It was not a bacterial infection and had no relation to infectious mononucleosis. The disease was neither yellow fever nor a modified form of yellow fever. The virus of yellow fever was not recovered from any material (blood, bile, urine, liver) from jaundiced patients.

The search for the icterogenic agent or factors is progressing along two main lines. One of these is an attempt to transmit the disease with materials derived from patients. The other is an attempt to reproduce it in animals with yellow fever vaccine or its components. Experiments are being conducted with the whole vaccine, vaccine with lot numbers known to have been associated with a high incidence of jaundice being used. Vaccine with lot numbers not associated with jaundice is used as a control. On the assumption that the component of human serum in certain lots of vaccine administered up to April 18, 1942 may have carried an icterogenic agent, the donor lists are being analyzed, and experimental inoculations may be made with the blood of some persons who contributed pools of serum. It will probably be impossible to attack directly the question whether the chick embryo component carried the icterogenic agent. Factors involving the operation of an organ-specific (liver) antigen-antibody system are also being investigated.

Patients with jaundice occurring several weeks or longer after they were vaccinated against yellow fever have in their serum antibodies capable of neutralizing the virus. It is shown from tests that jaundice has occurred in persons immune to yellow fever. On the other hand, the serum of a jaundiced patient who has not been given an injection of yellow fever vaccine does not possess these virus-neutralizing properties. The immunologic studies strengthen the conviction that an agent other than the virus of yellow fever was the cause of the jaundice or that a process other than the contact of the vaccine virus with the hepatic cells was the cause of the pathologic changes in the liver.

Epidemics of hepatitis and jaundice with clinical and pathologic manifestations similar to those observed in the outbreak now ending have occurred among troops in the armies of many nations in the past. During the first year of the Civil War there were 10,929 reported cases with 40 deaths among Northern troops. The French have referred to the disease as the "jaundice of camps," and the English have often called it the "jaundice of campaigns." There were 2,195 persons with epidemic hepatitis among British troops in the Mesopotamian-Dardanelles region from Sept. 5 to Nov. 6, 1915. It is a common enough disease of armies and

camps of young adults in civilian institutions. Reports have been received of the occurrence of jaundice in British and German troops in Africa and in troops of the United Nations in the Middle East and in India. Outbreaks of jaundice in civilian communities in this country and abroad have been well described in the past and are also subjects of recent reports. That jaundice of the usual so-called catarrhal type may have occurred and may be occurring among troops of the Army of the United States in certain locations is unquestionable. Such outbreaks among troops and civilians are characterized by an incubation period of twenty to thirty-five days or less and a spread by contact. As stated, the number of cases of jaundice of this type in the Army appears to have been about 125 per month in the first two months of this year. No extensive outbreak of jaundice in the civil population has occurred in this country in the past year.

From an epidemiologic standpoint the present outbreaks of hepatitis and jaundice in the Army showed the following special features:

(1) Simultaneous occurrence in troops in locations widely separated, from the Pacific to the Atlantic and from the North to the South, with notable intermediate locations.

(2) Absence of demonstrable contacts between these units.

(3) Invariable association of all large and many small outbreaks with the administration of certain lots of yellow fever vaccine.

(4) Predictable occurrence of the jaundice in groups of persons, troop units and others known to have received these lots of vaccine.

(5) Predictable occurrence of a certain percentage of cases of jaundice at stations to which troops known to have received certain lots of vaccine were dispatched.

(6) Occurrence of a certain percentage of cases of hepatitis and jaundice after an incubation period of seventy to ninety days following the administration of the aforementioned lots of vaccine. This incubation period extended from about forty to one hundred and twenty days, depending on lot numbers and conditions to which the patients were exposed. A few cases occurred as long as six months after vaccination.

(7) Occurrence of large numbers of cases of jaundice in large groups of persons vaccinated with one or the other of these lots and occurrence of few cases "in instances in which subdivisions of the groups received these lots while the more numerous group of 'contacts' free from jaundice received other lots of vaccine or were not vaccinated against yellow fever."

(8) Absence, to date of Sept. 5, 1942, of secondary outbreaks in locations at which this type of jaundice occurred. This has been true of places in which there were large numbers of cases following yellow fever vaccination and of places in which the patients with postvaccinal jaundice were in the midst of many times their number of nonvaccinated persons or persons vaccinated with nonicterogenic lots.

Examples could be multiplied. They are the basis for the conclusion that this outbreak was a type of jaundice following the administration of certain lots of yellow fever vaccine. The disease was not contagious and hence did not constitute a danger to the public health.

This epidemic was not confined to the experience of the military personnel, for similar observations on icterus following vaccination for yellow fever were reported by Fox and his associates from Brazil.[5] Once it was recognized that the epidemic of postvaccinal jaundice was due to an agent present as a contaminant

5. Fox, J. P.; Manso, C.; Penna, H. A., and Para, M.: Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68 (July) 1942.

in particular lots of vaccine and was not due to the virus of yellow fever used in the preparation of the vaccine, the method of preparation of the vaccine was changed and the epidemic of associated jaundice disappeared.

While a great number of cases developed, the mortality was slight. Fortunately, it was possible to eliminate the unidentified causative factor. Even if this had not been possible, this complication was of little importance compared with the seriousness of yellow fever in unvaccinated patients.

YELLOW FEVER

The foregoing observation is well emphasized by Soper,[6] as well as by Sawyer,[7] who summarized present knowledge of yellow fever in authoritative articles. They point out that yellow fever is a short, self-limited infection caused by a specific virus, followed by an intoxication due in large part to the destruction of tissue cells, especially the parenchymal cells of the liver.

The clinical picture of yellow fever may vary as much as does that of measles, smallpox, poliomyelitis or any other virus disease. Yellow fever may be seen as:

(*a*) An inapparent infection, recognized only through proof of acquired immunity.

(*b*) An abortive infection with vague initial symptoms suggestive of mild influenza, lasting only some hours or possibly one day, often recognized only by slowing of the pulse during convalescence.

(*c*) Incomplete attacks with severe onset, high fever, headache, body pains, dizziness and temperature and pulse curves typical of yellow fever but without hemorrhage, jaundice and anuria. Albuminuria and cylindruria may appear suddenly and increase rapidly on the third, fourth or even fifth day in the absence of other severe symptoms.

(*d*) Complete attacks with classic yellow fever. Following a typical onset with symptoms of severe infection, there occur during the second stage albuminuria, hemorrhage and jaundice. The classic attack may be mild if the hemorrhage does not become excessive and the kidneys continue to secrete. Severe oliguria and anuria are found only in cases presenting hemorrhage and jaundice.

The clinician notes in the early phase of classic yellow fever the usual signs and symptoms of acute infection but finds nothing to prepare him for the overwhelming intoxication which supervenes as the infection itself declines. The classic clinical picture of yellow fever is one of intoxication rather than of infection and consists of a symptom complex associated with the loss of hepatic and renal function, which is common to a number of diseases and intoxications producing destruction of hepatic parenchyma. This complex is not pathognomonic of yellow fever; it is the sequence of symptoms that is the most characteristic feature of the disease.

Period of Infection.—The onset of yellow fever is dramatic in the rapidity with which, within a period of a few hours, an apparently well person is transformed into a very sick patient. The symptoms—headache, backache, pain in the legs, malaise, nausea and vomiting—are out of all proportion to the physical findings. In many cases the infection is explosive; the pulse and the temperature reach their fastigia on the first day, after which there is a tendency for both to decline, the pulse falling sooner, more rapidly and more constantly than the temperature. This behavior of the pulse and the temperature is probably the most

6. Soper, F. L.: Treatment of Yellow Fever, J. A. M. A. **118**:374 (Jan. 31) 1942.
7. Sawyer, W. A.: Yellow Fever, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1939, vol. 5, pt. 2, pp. 731-738.

constant and characteristic individual finding in yellow fever. Although the temperature often shows a secondary rise during the phase of intoxication, the pulse seldom does, in uncomplicated cases, except at death. Bradycardia is common after the third day.

The general picture presented by the patient during the period of infection is one of active congestion accompanied by severe prostration. Nausea and vomiting, associated with this period, are not necessarily indicative of a serious prognosis, and the early appearance of relatively heavy albuminuria is of diagnostic rather than prognostic importance.

Generally, at the end of the first forty-eight to seventy-two hours the congestion declines, the temperature reaches normal or even subnormal levels and the patient enters a period of relative tranquility, which marks the end of the period of infection.

Period of Intoxication.—About the end of the third day, but sometimes as late as the fifth, the entire clinical picture changes. The active congestion of the previous period is replaced by venous congestion, accompanied by low arterial tension; nausea and vomiting, which may have been present during the period of infection, are now more severe and are of grave import. Overwhelming intoxication becomes apparent with the appearance of the formidable triad of albuminuria, hemorrhage and jaundice. In fulminant attacks the symptoms of intoxication are precocious and merge with those of the phase of the infection.

Jaundice.—The jaundice may be so slight as to be missed by an inexperienced observer and is rarely or never intense in the early stages. Subicterus is the most common finding and may be noted in the conjunctivas as early as the end of the second day, but severe, visible cutaneous icterus appears late and is not found in the fulminant type of the disease in which symptoms of intoxication appear before those of infection have abated.

Hemorrhage.—The amount of hemorrhage varies greatly, but some tendency toward hemorrhage is to be found in the majority of clinically diagnosable cases. Although slight hemorrhage may, and often does, occur during the initial stage of active congestion, the dangerous, typical hemorrhage of yellow fever is that of the second phase. Hemorrhage may be so severe as practically to exsanguinate the patient and is undoubtedly often the immediate cause of death.

Proteinuria.—The onset of proteinuria is rapid, as if some sudden violent intoxication involving renal function had occurred rather early in the course of the infection. It is almost a constant finding in cases of yellow fever, and even cases of mild involvement will usually show some protein in the urine. Practically all cases of severe yellow fever show much heavier proteinuria than would be expected in severe fevers due to other causes.

Anuria, the most dreaded symptom, may occur unexpectedly in cases presenting an otherwise favorable prognosis. Anuria apparently depends on an entirely different mechanism from that producing precocious proteinuria. The former is never found without other signs of destruction of the liver, whereas the latter may be heavy in cases of mild disease without such signs. Anuria follows and seems to depend on hepatic involvement; proteinuria may precede and even be independent of other signs of hepatic intoxication. It is probably safe to conclude that proteinuria may occur either directly as a result of involvement of renal function during the phase of infection or later because of intoxication secondary to destruction of hepatic parenchyma but that anuria is produced only by this secondary intoxication.

Studies on rhesus monkeys infected with yellow fever show the following early changes, which may appear some days before death: an increase in the bilirubin content of the blood; a decrease in the rate of excretion of bromsulfalein; a lowering of the fibrinogen content of the blood, associated with an increase in the clotting time. The later changes, generally apparent only on the last day before death, include: progressive hypoglycemia, becoming severe in later stages; a high concentration of nonprotein nitrogen in the blood; an absolute increase in urea concentration, proportionately less than the increase in nonprotein nitrogen; an increase of amino acid nitrogen, proportionately greater than the increase of nonprotein nitrogen; an increase of rest nitrogen. Creatinine increases but little, and that only immediately before death, probably as the result of terminal anuria; uric acid does not increase at all.

Only if yellow fever has produced obvious symptoms of intoxication do the concentrations of the nitrogenous constituents of the blood become appreciably altered. The most significant change is in the amino acid nitrogen, which shows strikingly large gains both absolutely and in relation to total nitrogen. The changes noted indicate a loss of ability to deaminize amino acids and to form urea, a deficiency of uric acid production and an impairment of the formation of hepatic glycogen, all of which are found following hepatectomy. It is difficult to escape the conclusion that they are dependent on destruction of the hepatic parenchyma. Although the kidneys are functionally damaged, the retention by the kidneys of the rhesus monkey of the ability to produce urine in normal amounts and normal concentration throughout the preintoxication stage of yellow fever indicates that this damage is not the chief factor in the production of the most characteristic disturbances of the disease. No definite evidence of serious impairment of renal function was observed except terminal anuria.

Autopsy generally reveals jaundice, hemorrhage, a pale yellow, fatty liver, a pale, flabby heart and tense, swollen kidneys. Greater or lesser evidence of hemorrhage may be found in the stomach, intestine, gallbladder, epicardium and pericardium, meninges, uterus, pleura, lungs and bladder.

Microscopic Changes.—The most important microscopic lesions of yellow fever consist of degenerative changes (fatty degeneration and necrosis of the parenchyma) with almost no inflammatory reaction. Many organs and tissues are affected by these changes, but those of the liver, kidneys and heart are most important.

(*a*) Liver: The extent of hepatic injury revealed by microscopic examination is surprising in the face of the relatively normal gross appearance of the liver. The degree of necrotic change may range from 5 to 95 per cent of the parenchymal cells. In extreme injury only a few cells recognizable as hepatic parenchyma may be found; some of these are seen close to the portal sheath at the periphery of the lobule, and a few others form a rim of scattered cells about the central vein. Fatty changes are always found, but the extent of involvement varies widely from patient to patient. There is no evidence of damage to the stroma.

(*b*) Kidneys: The reaction of the kidneys to yellow fever is like that of the liver: degenerative, not inflammatory. The lesion varies greatly from cloudy swelling to severe fatty degeneration and necrosis and is not necessarily correlated with the alterations of renal function observed. The convoluted tubules of the cortex are especially subject to damage, but the medullary tubes may also suffer. The glomeruli may show congestion and some exfoliation of surface epithelium.

(*c*) Heart: Well defined degenerative, noninflammatory changes may be found in all parts of the myocardium. Granular and fatty degenerations of the muscular

fibers are constantly found, hyaline and vacuolar degenerations less frequently. The degenerative lesions of the myocardium are sufficient to explain the functional disturbances encountered in yellow fever, such as bradycardia, lowered arterial pressure, severe asthenia, venous stasis and electrocardiographic irregularities.

The lesions are not equally severe in all organs of the same patient. When the liver is badly damaged, the heart may escape lightly, or vice versa, while in other instances the kidneys seem to bear the brunt of the attack. There is, however, in all cases resulting in death an appreciable necrosis of liver tissue, and this is the most constant as well as the most characteristic lesion of yellow fever.

Prophylaxis.—Soper stresses the necessity of achieving prophylaxis both by the eradication of yellow fever mosquitoes and by vaccination with the production of active immunity. According to tests, the immunity has lasted unchanged for the four year period since the present vaccine was introduced. Prophylaxis is important, for there is no specific treatment. Instead Soper quotes the aphorism of the Brazilian authority Sinval Lins [8]: "The therapy of yellow fever can be given in a single line—The disease cures itself or kills in spite of any and every treatment."

The difficulty in differentiating yellow fever from other types of jaundice and the presence of the latter in tropical areas are emphasized by Smith,[9] who reports a series of 14 cases of jaundice occurring in West Africa. The clinical findings in these cases suggested the diagnosis of yellow fever, but the microscopic examination of the liver made it possible to exclude the latter diagnosis.

LEPTOSPIROSIS ICTEROHAEMORRHAGICA

Leptospiral jaundice (Weil's disease) was confused with yellow fever in the early days of the search for the causative agent of yellow fever. The two diseases are now readily distinguishable by laboratory methods. Cases of leptospiral jaundice (Weil's disease) continue to be recognized and reported in this country in increasing numbers. Wilen, Snavely and Bruno [10] and Durand [11] have reported cases from New Orleans. Lester and his associates [12] have described a group of 14 cases from a coal mine in Alabama. Two have been reported from Philadelphia by Kramer [13] and 10 from New York by Tiffany and Martorana.[14]

The importance of agglutination tests in the identification of the disease is stressed by Packchanian [15] and by Tiffany and Martorana.[14] Jahn and Ludwig [16] have reported a case in which dark field examination of the blood showed leptospiral bodies. Many more organisms were found in the duodenal drainage, where they persisted until the twentieth day of the disease. This observation promises

8. Lins, S., cited by Soper.[6]

9. Smith, E. C.: Hepatic Findings Excluding Yellow Fever in Fourteen Cases of Jaundice in West Africa, Ann. Trop. Med. **36**:38 (June 30) 1942.

10. Wilen, C. J.; Snavely, J. R., and Bruno, F. E.: Report on Recently Observed Cases of Weil's Disease, New Orleans M. & S. J. **94**:338 (Jan.) 1942.

11. Durand, J. A.: Weil's Disease (Spirochetal Jaundice), New Orleans M. & S. J. **94**: 341 (Jan.) 1942.

12. Lester, B. S.; Denison, G. A.; Posey, L. C., and Tate, G. M.: Weil's Disease: Clinical and Epidemiological Report of Fourteen Cases, South. M. J. **35**:325 (April) 1942.

13. Kramer, D. W.: Weil's Disease: Incidence, Diagnosis and Treatment; Report of Two Cases, Pennsylvania M. J. **45**:1298 (Sept.) 1942.

14. Tiffany, E. J., and Martorana, N. F.: Leptospirosis in New York City: Serological Survey, Am. J. Hyg. **36**:195 (Sept.) 1942.

15. Packchanian, A.: Positive Agglutination Tests in Suspected Cases of Weil's Disease, Pub. Health Rep. **56**:2145 (Nov. 7) 1941.

16. Jahn, F., and Ludwig, E.: Demonstration of Spriochetes by Means of Dark Field in Duodenal Juice in Weil's Disease, Deut. Militärarzt **6**:274 (May) 1941.

to be of diagnostic aid in doubtful cases of jaundice. However, Jahn and Ludwig point out that the diagnosis of leptospirosis made by dark field examination should always be confirmed by animal inoculation or serologic tests before being accepted as conclusive.

INFECTIOUS AND TOXIC FORMS OF JAUNDICE

The various infectious and toxic forms of jaundice have been reviewed by Ottenberg and Spiegel.[17] They make a distinction between hepatic degeneration and jaundice due to infection and jaundice due to chemicals (table). The infectious forms of jaundice are again divided into groups depending on the nature of the hepatic degeneration—whether it is a dominant or an incidental feature of the clinical picture. Ottenberg summarizes an extensive literature and reemphasizes the observation that simple jaundice may progress to acute yellow atrophy. The chief difference between these two conditions is one of degree rather than of kind. The role of virus infections in both conditions is stressed, as is the probability that several different viruses may produce this clinical picture. While the gross similarities in the clinical pictures of the various types of infectious jaundice are well known, Ottenberg calls attention to the latent period before the appearance of the jaundice in epidemic acute yellow atrophy, yellow fever and leptospirosis. A similar latent period is observed after the introduction of some chemical poisons. Following recovery, a specific immunity is observed in the various types of infectious jaundice. In contrast, after recovery from chemical jaundice there is a greater sensitivity to many hepatotoxic agents.

Hepatic parenchymal diseases are classified by Ottenberg and Spiegel[17] as follows:

I. Infections causing degeneration of the liver and jaundice.
   A. Infections in which hepatic degeneration is a dominant feature.
      1. (*a*) Simple jaundice; (*b*) acute yellow atrophy.
      2. Leptospirosis.
      3. Yellow fever.
   B. General infections associated occasionally with jaundice.
      1. Lobar pneumonia.
      2. General septicemia.
      3. Syphilis.
      4. Tuberculosis.
      5. Acute infectious mononucleosis.
      6. Malaria.
      7. Oroya fever.

II. Jaundice due to chemicals.
   A. Direct injury to liver parenchyma.
      1. Therapeutic agents: gold, chloroform, arsenic, carbon tetrachloride, ether, iodoform, avertin, etc.
      2. Accidental contacts: amanitotoxin, nitrobenzene, phosphorus, burns, etc.
      3. Industrial hazards: tetrachlorethane, carbon disulfide, trinitrotoluene, etc.
      4. Experimental agents: selenium, copper, etc.
   B. Primary hemolysis with secondary injury to the liver cells.
      1. Therapeutic agents: phenylhydrazine, sulfonamide compounds, incompatible blood in transfusions.
      2. Accidental contacts: snake poison, bean poison.
      3. Industrial hazard: arsine.
      4. Experimental agents: distilled water, toluendiamine.
   C. Idiosyncrasy, hypersusceptibility and allergic sensitivity.
      1. Therapeutic agents: arsphenamine, cinchophen, liver extract, bismuth, sulfonamide compounds, mercury.

17. Ottenberg, R., and Spiegel, R.: The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents, Medicine **22**:27 (Feb.) 1943.

PORTAL CIRRHOSIS

A comprehensive study of portal cirrhosis has been reported by Ratnoff and Patek.[18] Records of 386 patients from various New York hospitals were analyzed with reference to the presence of antecedent factors, the chief symptoms and signs, the complications of cirrhosis, the prognosis as to life after the development of specific signs and the causes of death. In addition they give a critical review of much of the pertinent medical literature.

In this survey they found an increased incidence of cirrhosis in patients of Italian and Irish stock, though there was no convincing evidence of hereditary predisposition. Characteristically it appears in late middle life (40 to 65 years). Men were affected two to three times as often as women, perhaps because of the greater frequence of alcoholism in men. A study of dietary factors emphasized the importance of an antecedent deficiency to which the alcoholism may well have contributed. In a smaller group of cases syphilis, exposure to arsenic, malaria, typhoid and paratyphoid fevers, acute hepatitis and thyroid disease appeared to be possible contributory factors.

The initial clinical symptoms usually were flatulent dyspepsia and swelling of the abdomen. Loss of weight was the most frequent symptom and occurred in one half of the cases. Hematemesis occurred in about one quarter of the group. The frequency of other signs is presented in detail.

The chief signs of portal cirrhosis were ascites, edema, jaundice, a palpability of the liver or spleen, fever and evidences of collateral circulation. The role of portal hypertension and of a reduction in the serum albumin in the production of ascites was discussed. Jaundice frequently was a terminal phenomenon. Ratnoff and Patek stress the frequency of peripheral neuritis and its relationship to associated nturitional deficiencies.

Ascites, jaundice and hematemesis were all of serious prognostic import. Because of the size of the series it was possible for these authors to publish survivorship curves, showing the survival after the onset of each of these events. In each instance less than one third of the patients survived the first years.

The immediate cause of death was hepatic failure or cholemia in 35 per cent of the cases. This usually was accompanied by jaundice. Hematemesis was the terminal episode in one fourth of the cases. In another quarter of the cases death was due to secondary infections.

The treatment of cirrhosis by high vitamin, high protein, low fat diets is discussed by Patek and Post [19] and by Fleming and Snall.[20] Both groups of investigators report encouraging results in their series of cases. Not only was the clinical course of the disease influenced favorably but there was an increased period of survival in the treated as compared with the control groups of patients. While the results were encouraging, it must be remembered that the effects were slow. It took time for improvement in nutrition as well as for regeneration of hepatic tissue.

The dietary treatment of patients with cirrhosis therefore represents only one phase of the management of the condition. The various factors in the control of

18. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis of the Liver: An Analysis of Three Hundred and Eighty-Six Cases, Medicine **21**:207 (Sept.) 1942.

19. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Investigation **20**:481 (Sept.) 1941.

20. Fleming, R. G., and Snell, A. M.: Portal Cirrhosis with Ascites: An Analysis of Two Hundred Cases with Especial Reference to Prognosis and Treatment, Am. J. Digest. Dis. **9**:115 (April) 1942.

ascites and hemorrhage and in the symptomatic management of ascites and of portal cirrhosis are reviewed by Greene.[21] The indications for administration of mercurial diuretics with added acid salts, such as ammonium chloride or ammonium nitrate, for paracentesis, for giving liver extract, for transfusions, for vitamin K therapy and for omentopexy are discussed. He reports that in selected cases infusions of ascitic fluid seemed to have some value in conserving plasma protein and in treating hypoproteinemia.

The greater part of the earlier literature on the experimental production of hepatic cirrhosis by dietary measures was reviewed last year.[21] Further experiments have been reported by Daft, Sebrell and Lillie and their associates,[22] showing that in rats neither a high fat diet nor one containing free cystine was essential for the production of hepatic cirrhosis. They found that choline, methionine or casein in sufficient amounts would prevent the development of cirrhosis or, if given after the cirrhosis had developed, would favor regeneration of hepatic cells and improvement in the clinical condition of the animals. These experiments therefore parallel the clinical observation of Broun and Muether.[23]

THE LIVER IN RELATION TO PROTEIN METABOLISM

The relation of the liver to protein metabolism has long been recognized, but knowledge regarding details is increasing rapidly at the present time. The paramount role of the liver in the deaminization of amino acids and the synthesis of urea is well known. The part played by the liver in the synthesis of serum proteins, especially of serum albumin, and the association of hypoalbuminemia with hepatic cirrhosis are recognized.[24] The effects of high protein diets in protecting the liver from toxic injury by such substances as chloroform and in preventing cirrhotic changes in experimental animals on special diets have been discussed.

Evidence has gradually been accumulated to show that the body contains considerable stores of protein and that the liver is one of the principal storehouses. This was suggested by Pflüger[25] and Seitz[26] and demonstrated by Addis and his associates[27] and by Luck.[28] The reserve stores of protein in the liver are increased by a high protein diet and decreased by fasting. According to Addis,

21. Greene, C. H.: Physiological Considerations in the Treatment of Portal Cirrhosis, J. A. M. A. **121**:715 (March 6) 1943; Liver and Biliary Tract: A Review for 1941, Arch. Int. Med. **69**:691 (April) 1942.

22. Daft, F. S.; Sebrell, W. H., and Lillie, R. D.: Prevention by Cystine or Methionine of Hemorrhage and Necrosis of the Liver in Rats, Proc. Soc. Exper. Biol. & Med. **50**:1 (May) 1942. Lowry, J. V.; Daft, F. S.; Sebrell, W. H.; Ashburn, L. L., and Lillie, R. D.: Treatment of Dietary Liver Cirrhosis in Rats with Choline and Casein, Pub. Health Rep. **56**:2216 (Nov. 14) 1941. Lillie, R. D.; Ashburn, L. L.; Sebrell, W. H.; Daft, F. S., and Lowry, J. V.: Histogenesis and Repair of the Hepatic Cirrhosis in Rats Produced on Low Protein Diets and Preventable with Choline, ibid. **57**:502 (April 3) 1942.

23. Broun, G. O., and Muether, R. O.: Treatment of Hepatic Cirrhosis with Choline Chloride and Diet Low in Fat and Cholesterol, J. A. M. A. **118**:1403 (April 18) 1942.

24. Post, J., and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: I. Relation to Prognosis and Formation of Ascites, Arch. Int. Med. **69**:67 (Jan.) 1942; II. Nitrogen Balance Studies on Five Patients, ibid. **69**:83 (Jan.) 1942.

25. Pflüger, E.: Glykogen, Arch. f. d. ges. Physiol. **96**:1, 1903.

26. Seitz, E.: Die Leber als Worrathskammer für Eiweisstoffe, Arch. f. d. ges. Physiol. **111**:309, 1906.

27. Addis, T.; Lee, D. D.; Lew, W., and Poo, L. J.: The Protein Content of the Organs and Tissues at Different Levels of Protein Consumption, J. Nutrition **19**:199 (Feb.) 1940. Addis, T.; Poo, L. J., and Lew, W.: The Quantities of Protein Lost by Various Organs and Tissues of the Body During a Fast, J. Biol. Chem. **115**:111 (Aug.) 1936.

28. Luck, J. M.: Proteins: I. The Question of Protein Storage, J. Biol. Chem. **115**:491 (Sept.) 1936.

the gain or the loss may amount to some 40 per cent of the protein in the liver. The accumulated evidence on this topic was reviewed by Luck in 1938.[29]

Since then Elman and Heifitz [30] have shown that when dogs are made hypoproteinemic by a protein-deficient diet, the protein content of the liver is reduced. Histologic changes in the liver could be correlated with the reduction in the protein.

More recently Elman, Smith and Sachar [31] have reported that following protein starvation the histologic appearance of the liver, as well as its content of nitrogen and glycogen, depends on the intake of carbohydrate. When the intake of carbohydrate is high, the cells are large, contain little protein and present a rarefied appearance of the cell cytoplasm often called hydropic degeneration.

After a fast (absence of carbohydrate), the liver is just as deficient in total nitrogen because it is smaller, although the concentration thereof is normal. The microscopic picture may be called one of atrophy. The cells are smaller, the nuclei closer together and the cytoplasma dense.

These observations are significant in showing the magnitude of the changes in the cytologic appearance of the liver in consequence of differences in diet, with resultant changes in the size and the chemical composition of the liver. The role of similar changes in the chemical composition of the liver must be kept in mind in interpreting the appearance of pathologic sections.

Interpretations such as this are based on the assumption that the hepatic cell consists of a unit of protoplasm that represents the basal protoplasmic constituents essential to life and continued function of the cell. Superimposed on this basic material are reserves or stores of protein, fat and glycogen possibly with varying amounts of bound water. So far no investigator has been able to determine these different materials with accuracy. Until that can be done, the interpretation of changes in the chemical composition of the liver is difficult because it is not possible to decide whether the percentage changes are due solely to shifts in the amounts of stored reserves or are due also to changes in the number of parenchymal cells. The use of colonies of rats of uniform age and size will permit statistical analysis of changes in the gram weight of the liver and give a quantitative measure of the total changes found. But until this is combined with a measure of the protoplasmic units, complete analysis is not possible.

For many years a satisfactory parenteral method of supplying protein to the body has been sought. This problem has apparently been solved in two ways. One way is by the use of blood plasma. The benefit of plasma in preventing wound shock has been one of the outstanding developments of military medicine in the present war. Plasma, however, is expensive and without the pressure of the wartime emergency, it would not be so readily obtainable. Various protein digests have been studied, and it has been shown that a patient can be kept in nitrogen equilibrium by intravenous injection of amino acids. The extensive literature on this topic has been reviewed by Martin and Thompson [32] in detail. Most of the literature has dealt with the use of this therapy in various medical and surgical conditions. Goettsch, Lyttle, Grim and Dunbar [33] found that in dogs fed a very low protein diet a progressive hypoproteinemia developed. When amino acids were

29. Luck, J. M.: The Liver Proteins, in Needham, J., and Green, D. E.: Perspectives in Biochemistry, London, Cambridge University Press, 1938.

30. Elman, R., and Heifitz, C. J.: Experimental Hypoalbuminemia, J. Exper. Med. **73**:417 (March) 1941.

31. Elman, R.; Smith, M. G., and Sachar, L. A.: Correlation of Cytological with Chemical Changes in the Liver as Influenced by Diet, Particularly Protein, Gastroenterology **1**:24 (Jan.) 1943.

32. Martin, G. J., and Thompson, M. R.: Intravenous Alimentation with Amino Acids, Medicine **22**:73 (Feb.) 1943.

injected intravenously into these animals the retention of these substances was proportional to the decrease in the serum albumin. Goettsch and her associates interpret this as evidence of impairment of hepatic function. Changes of equal severity are not likely to be seen clinically for Stewart and Rourke [34] found that intravenous infusions of amino acid mixtures were equally well utilized by normal persons and by patients with various diseases of the liver and biliary tract.

Fagin and Zinn [35] report good results in 5 patients with hepatic cirrhosis who received amino acid mixtures intravenously. No controls were used, so that it is not possible to decide whether these beneficial responses were due to the amino acid mixtures or to the general measures which were undertaken at the same time. The work of Goettsch and her associates and that of Post and Patek have suggested that the severely damaged liver cannot utilize amino acids at a normal rate, whether these are parenteral or digestive in origin. Response to therapy then must depend on improvement in the general nutritional condition of the patient rather than on a specific effect of the injected amino acids.

THE MANAGEMENT OF THE TYPHOID CARRIER

The control of typhoid fever in many states has reached the point where contaminated water, milk and food no longer are of significance in the spread of the disease. Under these conditions carriers of typhoid bacilli become the chief factor in the maintenance of the infection. Control of these carriers is therefore of paramount importance to public health. The carriers may harbor the bacilli in the gallbladder, the biliary ducts, the intestine or the urinary tract. Biliary carriers are the most frequent and can be recognized by culturing the bacilli from the duodenal drainage.

To date no satisfactory biliary antiseptic has been reported. Hanssen [36] summarized the findings in this field in 1939 and reported that cholecystectomy was the most successful method of eradicating the carrier state. He reported cure in 85 per cent of 160 cases collected from the literature. Additional cases have since been reported by Elsom and her associates [37] and by Coller and Crabtree [38] among others. Elsom reported that roentgen therapy was entirely ineffective in eradicating the infection.

Tetraiodophthalein sodium was shown by Nickel [39] to have some bacteriostatic action. Onodera and his associates [40] and Saphir and Howell [41] later reported

33. Goettsch, E.; Lyttle, J. D.; Grim, W. M., and Dunbar, P.: Amino Acid Studies: I. Plasma Amino Acid Retention in the Hypoproteinemia Dog as Evidence of Impaired Liver Function, J. Biol. Chem. **144**:121 (June) 1942.

34. Stewart, J. D., and Rourke, G. M.: Changes in Blood and Urine After Intravenous Amino Acid Mixture in Patients with Liver Disease, Proc. Soc. Exper. Biol. & Med. **51**:364 (Dec.) 1942.

35. Fagin, I. D., and Zinn, F. T.: Cirrhosis of the Liver: Results of Treatment with Parenterally Administered Amino Acids, J. Lab. & Clin. Med. **27**:1400 (Aug.) 1942.

36. Hanssen, E. C.: The Present Status of the Typhoid Carrier Problem, New York State J. Med. **39**:1347 (July 15) 1939.

37. Elsom, K. O'S.; Miller, S. G.; Forrester, J. S., and Chamberlin, G. W.: Radiation and Cholecystcetomy as Therapeutic Procedures for Typhoid Carriers, Am. J. M. Sc. **194**:466 (Oct.) 1937.

38. Coller, F. A., and Crabtree, P.: Chronic Biliary Typhoid Carriers, Surgery **12**:426 (Sept.) 1942.

39. Nickel, A. C.: Tetiothalein Sodium—N. N. R. (Tetraiodophenolphthalein) as an Antiseptic and Germicide of the Biliary Tract, J. Pharmacol. & Exper. Therap. **37**:359 (Nov.) 1929.

(Footnotes continued on next page)

a germicidal action of soluble iodophthalein (tetraiodophenolphthalein sodium) on the typhoid bacillus. Saphir and Howell reported a carrier of paratyphoid bacilli and Enright [42] a carrier of typhoid bacilli apparently cured by treatment with soluble iodophthalein. Saphir, Baer and Plotke [43] continued these studies on a series of 110 carriers of typhoid bacilli. Sixty-five of these were established to be biliary carriers. In 21 of these, or one third, cultures of the duodenal drainage became negative after treatment. The carrier state, however, was not cured, for an intestinal carrier state was present in the majority of instances. Only 7.6 per cent of the persons studied were cured of their carrier state by treatment with soluble iodophthalein.

Cutting and Robson [44] have reported a series of 6 carriers of typhoid bacilli and 1 carrier of dysentery bacilli who were not cured by treatment with thionol (3-oxo-7-hydroxy-3-isophenothiazine), phenothiazine, soluble iodophthalein, sulfaguanidine (sulfanilylguanidine) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). Ames [45] also has reported a series of 8 carriers of typhoid bacilli treated with soluble iodophthalein without success.

The treatment of the carrier of typhoid bacilli with sulfaguanidine was initially advocated by Levi and Willen.[46] They administered this drug to a carrier who had typhoid bacilli in both the biliary and the intestinal tract and who continued to have positive cultures of the stools after cholecystectomy. The continuous administration of sulfaguanidine for a week apparently cured this carrier. The effectiveness of sulfaguanidine could not be confirmed by Saphir, Baer and Plotke [43] or by Cutting and Robson.[44] Hoagland,[47] however, has reported successful results in 2 cases. He points out that sulfaguanidine can be effective only in intestinal carriers. The value of this compound in the treatment of intestinal typhoid bacillus carriers is still undecided, but the need for careful selection of the patients in which it is to be tried is apparent.

It is evident, therefore, that at present there is no dependable or efficient curative agent for the eradication of the typhoid carrier state. Control of the carrier by established methods must continue. This rule applies to the biliary carrier as well as to the carrier in whom the exact locus of the bacilli has not been determined. However, the reviewer agrees with Saphir, Baer and Plotke [48] that when a carrier shows typhoid bacilli in the bile obtained by duodenal drainage, and cholecystograms show a normally functioning gallbladder without stones, a trial of soluble iodophthalein is indicated. Treatment with soluble iodophthalein

40. Onodera, N.; Murakawa, G., and Liu, S.: Ueber eine neue Behandlung von Typhus Bazillentragern, Deutsches Arch. f. klin. Med. **171**:503, 1931.

41. Saphir, W., and Howell, K. M.: Soluble Iodophthalein in Treatment of Carriers of Typhoid: Paratyphoid Group, J. A. M. A. **117**:1988 (May 18) 1940.

42 Enright, J. R.: Apparent Cure of a Typhoid Carrier with Soluble Iodophthalein, J. A. M. A. **116**:220 (Jan. 18) 1941.

43. Saphir, W.; Baer, W. H., and Plotke, F.: The Typhoid Carrier Problem: Report of a Study of One Hundred and Ten Typhoid Carriers at the Manteno State Hospital, Manteno, Ill., J. A. M. A. **118**:964 (March 21) 1942.

44. Cutting, W. C., and Robson, G. B.: The Alleged Efficiency of Medicinal Treatment of Typhoid Carriers, J. A. M. A. **118**:447 (April 25) 1942.

45. Ames, W. R.: Treatment of Typhoid Carriers, J. A. M. A. **119**:1217 (Aug. 8) 1942.

46. Levi, J. E., and Willen, A.: The Typhoid Carrier State Treated with Sulfaguanidine, J. A. M. A. **116**:2258 (May 17) 1941.

47. Hoagland, R. J.: The Typhoid Carrier State Treated with Sulfaguanidine, J. A. M. A. **120**:1211 (Dec. 12) 1942.

48. Saphir, W.; Baer, W. H., and Plotke, F.: Treatment of Typhoid Carriers with Iodophthalein, J. A. M. A. **119**:582 (June 13) 1942.

without first establishing the condition of the gallbladder and biliary tract is irrational and uneconomical, for only a small proportion of carriers of typhoid are really suitable for such a trial.

DISEASE OF THE GALLBLADDER

Various discussions of chronic cholecystitis have appeared, but no attempt will be made to review those dealing with surgical statistics or the general features of chronic cholecystitis. The tendency rather has been to emphasize the importance of biliary dyspepsia, as in the article of Holroyd.[49] A similar point of view is held by Moser and his associates,[50] who point out that the colic of gallbladder disease usually is relieved by cholecystectomy but that the dyspepsia is not. They insist, therefore, that dyspepsia alone should not be an indication for cholecystectomy.

Similar discussions relative to disturbances in the common duct have been presented by Best [51] and Wilensky.[52] The most comprehensive survey of gallbladder disease is that of Russell, Carter and Oppenheim,[53] who discuss the cause, the diagnosis and the treatment of diseases of the gallbladder in detail. In this discussion they have introduced several concepts not ordinarily considered.

The usual point of view, as presented for example by Walters and Snell,[54] is that

> . . . no form of cholecystic disease, gallstones in particular, appears as a primary disorder; there must be an initial injury to the structure of the gallbladder, which in turn may develop to the point of complete functional incapacity, formation of stone or state of chronic infection, present individually or in combination. The nature of these hypothetic initial injuries never has been satisfactorily determined; one or several factors may be responsible. There is much to suggest that the typical stone-bearing functionless and infected gallbladder seen by the surgeon at operation may have arrived at its condition by any one of several different routes. Once the normal physiologic properties of the gallbladder have been disturbed a host of factors pertaining to infection, motor disturbances and alterations in the chemical constituents of the bile may become operative to perpetuate and advance a pathologic process. For the aforementioned reasons it is necessary to consider first the mechanisms by which the initial damage is done and then to examine the evidence bearing on the further development of the pathologic process.
>
> The subject of initial injury to the gallbladder may be considered from the standpoint of (1) infection, (2) disturbances in cholesterol metabolism produced in various ways, and (3) mechanical, toxic and chemical factors.

Russell, Carter and Oppenheim [53] attempt to define this initial factor and have sought for the earliest evidence thereof. They find that anatomic and physiologic abnormalities frequently precede and serve as a basis on which disease processes develop. They therefore look on gallstones, infection and cholecystitis as organic lesions developing on an underlying disturbance in structure or function. Treatment, to be successful, must be directed toward the basic functional disturbance as well as toward the engrafted organic complication.

They therefore emphasize that disease of the gallbladder is progressive. Whatever the initiating process, be it functional or organic, time adds factors such as gallstones, infection, obstruction or obliteration of the gallbladder. If the

49. Holroyd, F. J.: Biliary Dyskinesia, West Virginia M. J. **37**:407 (Sept.) 1941.

50. Moser, R. H.; Rosenak, B. D., and Hasterlik, R. J.: Gallbladder Dyspepsia, Am. J. Digest. Dis. & Nutrition **9**:49 (Feb.) 1942.

51. Best, R. R.: Management of Common Duct Lesions, Nebraska M. J. **26**:5 (Jan.) 1941.

52. Wilensky, A. O.: The Danger of Procrastination in Biliary Tract Disease Until Irreversible Liver and Kidney Changes Occur, Am. J. M. Sc. **203**:231 (Feb.) 1942.

53. Russell, T. H.; Carter, R. F., nad Oppenheim, E.: Gallbladder Disease: Etiology, Diagnosis and Treatment, Bull. New York Acad. Med. **19**:77 (Feb.) 1943.

54. Walters, W., and Snell, A. M.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940.

influence of the initiating factor is extended to the common duct, then stones in the common duct, infection and cholangitis, biliary obstruction and hepatic cirrhosis may eventually develop.

They classify diseases of the gallbladder into three main groups on the basis of the different etiologic factors concerned, as follows:

I. Disorders resulting in disturbances of the filling and emptying mechanism of the gallbladder.
   A. Anatomic causes (mechanical).
      1. External—congenital or acquired.
         (*a*) Adhesions—congenital or inflammatory.
         (*b*) Abnormal cystic artery.
         (*c*) Pancreatic inflammation—edema, fibrosis with involvement of the common duct.
         (*d*) Tumors of the pancreas and the extrahepatic bile ducts.
      2. Internal—all congenital.
         (*a*) Convoluted cystic duct—valve of Heister obstruction.
         (*b*) Septums—phrygian cap.
   B. Physiologic causes (functional).
      1. Hypertonic dyssynergia.
      2. Hypotonic dyssynergia.

II. Disorders resulting in disturbances of the concentrating function of the gallbladder.
   A. Infectious cholecystitis.
   B. Reflux of pancreatic juice.
   C. Abnormal concentration of special elements.
      1. Bile salts.
      2. Calcium—calcified wall of the gallbladder.
      3. Calcium carbonate—"milk of calcium" gallbladder.
      4. Cholesterol—cholesterosis.

III. Disorders in blood and metabolism resulting in disturbances of the gallbladder.
   A. Hemolytic jaundice—congenital hemolytic icterus, sickle cell anemia, etc.
   B. Cholesterol metabolism.
      1. Pregnancy.
      2. Obesity.

They then discuss the effects of each of these factors in detail with regard to their relative frequency, the special symptom complex when present, the characteristic diagnostic findings by duodenal drainage and roentgen examination. The medical and surgical treatment is outlined, and the progressive course of the disease in the untreated patient is discussed. The presentation is concise. In the opinion of the reviewer, it is the most satisfactory presentation of this whole field of disease of the gallbladder and biliary tract to date.

News and Comment

Meeting of American College of Chest Physicians Canceled.—At its midwinter meeting, held in Chicago on February 14, the Board of Regents of the American College of Chest Physicians voted to cancel the meeting of that association this year for the same reasons that the 1943 Annual Session of the American Medical Association has been canceled.

The Board of Regents recommended that in those instances in which it is feasible state and district chapters of the college arrange to meet jointly with their state and district medical societies and assist in preparing scientific programs concerning the specialty of diseases of the chest.

Wartime Public Health Conferences.—The American Public Health Association will sponsor a three day Wartime Public Health Conference in New York, Oct. 12 to 14, 1943.

The program of the conference will be devoted exclusively to wartime emergency problems as they affect public health and the public health profession.

Book Reviews

Biological Symposia: Vol. IX, Sex Hormones. Edited by F. C. Koch and P. E. Smith. Price, $2.50. Pp. 146. Lancaster, Pa.: Jaques Cattell Press, 1942.

Volume IX is part of a series devoted to current symposiums in the field of biology. It contains four papers on the actions and metabolism of sex hormones, and four papers on hormonal factors in the inversion of sex.

Prof. Carl Moore, of the University of Chicago, presented the biologic introduction to the symposium on sex hormones. No one is better qualified to do this. It is his opinion that the testes and ovaries can be regarded as the principal, although not the exclusive, source of androgens and estrogens. These hormonal substances carry the principal responsibility for inducing the functional maturity of the male and the female complex, including the structural portions of the reproductive system, as well as the psychic or behavioral reactions. A specific genetic constitution to some extent different in the two sexes provides the background or framework on which the hormones operate. It has been abundantly demonstrated that the hormones exhibit considerable capacity to modify the normal expression of the opposite genetic constitution.

Dr. A. T. Kenyon, assistant professor of medicine, University of Chicago, wrote the next paper, entitled "The Comparative Metabolic Influences of the Testicular and Ovarian Hormones in Man." He expresses the belief that the androgens exert anabolic effects on tissues other than those of the genital system. He mentions growth in weight and height of the human body after injections of androgens. A rise in production of heat and retention of nitrogen also occur and with this, retention of the associates of nitrogen in protein formation.

Estradiol benzoate also induces reduction in urinary nitrogen, but the dose known to be effective is so large that it is not clear whether this effect is a physiologic manifestation of ovarian function.

The third paper is by Prof. E. A. Doisy on "The Metabolism of the Estrogens." He reviews the anabolism and catabolism of these hormones. In large measure because of the investigations of Doisy himself sufficient data, apparently based on substantial grounds, are now at hand to establish the sources of estrogens and the means by which their destruction is effected.

Prof. F. C. Koch treats androgens in a similar manner. His article contains several especially interesting paragraphs on changes in excretion of sex hormones in disease, including tumors of the adrenal glands and Addison's disease.

The bibliographies of both Doisy's and Koch's paper are lengthy, and no doubt contain the best papers relative to the biochemistry of estrogens and androgens.

Of the group of papers concerned with hormonal factors in the inversion of sex, the one by Dr. R. R. Greene on "The Effects of Sex Hormones on Embryonic Sexual Structures of the Rat" is outstanding. This work represents the combined efforts of Dr. M. W. Burrill, Dr. A. C. Ivy and the author in the departments of physiology, pharmacology and gynecology of Northwestern University Medical School. Their work seems to establish the fact that sex hormones can markedly modify the differentiation of the sexual structures in the rat embryo.

To obtain such effects, large amounts of the hormonal substance concerned must be administered to the pregnant rat. If the dose is sufficient, the substance is apparently able to traverse the maternal circulation, reach the embryo and modify its sexual development.

These papers on sex inversion contain experimental data and theories that apply primarily to the animals studied. Such work, however, is necessarily pertinent to any consideration of similar conditions in human beings. As is stated by one of the authors, the factors influencing the normal tendencies of the genotype are numerous and varied, but among them the hormones are of outstanding importance. In so far as it is possible in these short papers the authors evidence a critical and broad approach to the subject at hand. To interested persons this book is well worth careful reading and study.

Medical Parasitology. By James T. Culbertson, College of Physicians and Surgeons. Price, $4.25. Pp. 285, with 16 text figures and 21 plates. New York: Columbia University Press, 1942.

Recent years have seen the appearance of several American textbooks on animal parasitology, and this year they were augmented by Strong's comprehensive revision and enlargement of Stitt's textbook on tropical diseases and by Belding's book on clinical parasitology.

To the present time there had not appeared an authoritative "small book useful chiefly to medical students and medical practitioners, in which these persons will find a résumé of the significant information upon the animal parasites of medical importance." This gap the author seeks to fill.

The task is not an easy one, and Dr. Culbertson is to be congratulated on having presented a useful textbook. As was to be expected, in view of the author's special interests, the discussions of natural resistance, acquired immunity and immunologic procedures, though concise, are of particular value. Tabulations of such material as "the route of infection, final site of residence and chief effects of the important parasites of man," diagnostic procedures and drugs used for treating infections with animal parasites will be particularly appreciated by students concerned with term examinations.

There are numerous inaccuracies throughout the text, some of which are probably chargeable to proofreaders. Manson's suggestion of the significance of mosquitoes as vectors of filariasis was first made in 1877, not 1879; Glossina palpalis was shown to transmit sleeping sickness in 1903, although the development in the fly was demonstrated in 1909; the British Plague Commission in India in 1906 presented conclusive evidence of the role of fleas in the spread of plague, and it was promptly put to practical test in this country in 1907. Ross did not begin his studies first "in the malaria of birds," but for the first three years worked on malaria in human beings. On page 7 it is stated that "Leishmania were seen in 1900," but on page 90 one finds that "*Leishmania tropica* was probably first observed by Cunningham in 1885, but first accurately described by Borvosky, a Russian, in 1898." Since biopsy is looking at living tissue, one does not "decide to biopsy the spleen and look for Leishmania" (page 88).

In the discussion of the parasites themselves there are not a few statements which are open to question. It is inaccurate to state regarding Endamoeba histolytica that in dogs only trophozoites are procured. The author includes the mink as a host of Paragonimus westermani but does not mention the occurrence of lung flukes in North America. It is doubtful whether Cercaria elvae is as widely concerned with schistosome dermatitis as is Cercaria stagnicolae, although the latter species is not mentioned. In view of the careful experimental studies of Japanese investigators, it would seem overconservative to say regarding Hymenolepis nana that "it is not proved that man is infected from the rodent host or that rodents are infected from man." The discussion of Arthropoda of medical importance is especially sketchy, and the descriptions fall far short of giving enough morphologic information to "enable the student to identify and differentiate the organisms which are discussed."

Unfortunately, little aid in identification is afforded by the 140 photographs on 21 plates, distributed with little regard to the text which they are intended to illustrate. For this the publisher's desire to keep down costs of reproduction is doubtless largely responsible.

In spite of its deficiencies "Medical Parasitology" will be welcomed by many teachers and students on account of its concise, clearcut presentation of essential material relative to the important animal parasites of man.

Disease of the Liver, Gall-Bladder and Bile Ducts. By S. S. Lichtman, M.D. Price, $11, buckram. Pp. 906, with 122 engravings and a colored plate. Philadelphia: Lea and Febiger, 1942.

This book is a scholarly piece of work. The author has reviewed the literature of a complicated subject in a workman-like fashion and from this and his own experience has created an excellent textbook.

The early chapters deal with the most recent anatomic concept of the liver lobule. The illustrations of this are particularly good. Next is discussed the physiology of the liver, with appropriate attention to the relation to the biliary system of bilirubin, bile acids, bile salts and vitamins. Then such topics as exogenous hepatic poisons and the role of nutrition and diet in the management of hepatic disease are considered. The pathogenesis of jaundice and, in fact, of all pathologic conditions of the liver, is well described. Considerable emphasis is given to the cirrhoses, though all disorders of the liver and its appendages receive appropriate consideration.

The symptoms of disease of the biliary tract are discussed from the viewpoint of correlating as far as possible laboratory data with clinical experience. This proves an interesting method of approach. Another useful part of the book deals with a critical evaluation of the various tests now employable for estimating biliary function.

The author is conservative and sound in his views. His book promises to be popular with medical students and physicians. Certainly it can be recommended.

The Antigonadotropic Factor, with Consideration of the Antihormone Problem. By Bernhard Zondek and Felix Sulman. Price, $3. Pp. 185. Baltimore: Williams & Wilkins Co., 1942.

In this monograph Zondek and Sulman present a rather full discussion of the problem of the antigonadotropic problem. They not only include a review of the literature but describe a few unpublished observations of their own. The data are divided and discussed as follows: "Historical Review," "The Antihormone Theory of Collip," "The Antigonadotropic Factor," "Clinical Significance of the 'Antihormones'" and "Mechanism of the Antigonadotropic Reaction." The authors present evidence which they believe strongly indicates that the antigonadotropic substances are to be classified "as a group of immune bodies of a character hitherto unknown in serology."

The monograph should be of great interest not only to persons interested in endocrinology, but to physiologists, biochemists, immunologists and internists. It tends to emphasize the immunologic mechanisms of antigonadotropic activity instead of the point of view that an antagonistic hormone is secreted that neutralizes gonadotropic substances. Many aspects of this problem, obviously, will remain unanswered until the gonadotropic hormones and their "antagonists" are isolated in a chemically pure state.

Familial Nonreaginic Food-Allergy. By Arthur F. Coca. Price, $5. Pp. 160. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

Coca believes he has been able to delimit a group of cases of food allergy which differs in several respects from atopic ("reaginic") allergy: Allergic reagins or antibodies are not demonstrable by direct or indirect cutaneous testing; the hereditary influence controlling the occurrence of this type of allergy is independent of the atopic inheritance; many of the symptoms are not represented in the atopic group, and the allergic reaction practically always causes acceleration of the pulse. The symptoms of patients with such allergy are of extremely wide scope, ranging from physical fatigue to heartburn. Thus, their conditions comprise a wider range of ailments than is customarily accepted as being allergic in origin. Coca considers it possible in most instances to determine by means of the pulse rate all offending foods and other excitants with a high degree of accuracy. The method consists of establishing the basal pulse rate and its daily range. An increase of rate in excess of 14 beats a minute is thought to be diagnostic of antigenicity. This book will undoubtedly be considered provoking. The results of these studies will have to be repeated before these newer concepts and methods will be generally accepted.

Psychotherapy in Medical Practice. By Maurice Levine, M.D. Price, $3.50. Pp. 320. New York: The Macmillan Company, 1942.

The past few years have seen an increasing interest in psychosomatic medicine. This has led to the production of several new books each composed with the worthy object of making understandable to the general reader the essentials of modern psychiatry and psychotherapy.

It is a difficult matter for any author to write simply about any phase of how the mind works. Thus, certain attempts in this line have seemed to sacrifice completeness for the sake of simplicity or, on the other hand, have been too abstruse for the average physician or medical student.

Here is a useful compromise. The author has put together a practical book which is interestingly written so as to be readable and authoritatively written so as to be informative. It describes well the difficulties to be overcome in successful estimation of the effect of emotional disturbances on human relations and outlines the various methods of psychotherapy now available. It gives a well chosen list of references to current literature. On the whole, it is worth having in one's library.

Religion and Health. By Seward Hiltner. Price, $2.50. Pp. 292. New York: The Macmillan Co., 1943.

This is not a quack book but a thoughtful scholarly treatise by a serious student of the relation of religion to health. Granted that physicians now recognize the importance of physical and mental health, Dr. Hiltner would lay an additional emphasis on spiritual well-being and its place in the armamentarium of healing. While the point of view is developed against the background of Christian philosophy, the treatment is a broad one which goes to the roots of what spiritual aid can accomplish in helping a sick person. Young physicians especially, who perhaps have felt that physics and chemistry are enough to solve the problem of disease, would profit much from a careful reading of this book.